International Conference on Computational Cell Biology

August 14-16, 2013

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Dear Friends and Guests,

On behalf of the faculty, staff, and students of the College of Science, we welcome you to Blacksburg, Virginia. We are pleased to host the first International Conference on Computational Cell Biology on the Virginia Tech campus. We hope that this conference will provide a platform for exchanging scientific ideas, networking, and fostering new collaborations.

We recognize that life science is one of the leading research areas in this century. Our college is active in developing the program of quantitative and systems biology. Among several new initiatives we are putting in place at Virginia Tech is an initiative for a degree program in Systems Biology that starts with the Bachelor of Science, which will focus on approaches connecting the biochemical and genetic properties of individual macromolecules (DNA, RNA, protein, lipids, polysaccharides) with the physiological behavior of living cells and tissues. We will be happy to discuss this program further during the education session in the conference.

Again welcome and enjoy your stay at Blacksburg.

Best Regards,

Lay Nam Chang
Dean
College of Science
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Grants

We acknowledge generous support from the Army Research Office (ARO)

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College of Science - Department of Biological Sciences
Fralin Life Science Institute

Silver Level

Bronze Level

Office of Vice President for Research
Wednesday, August 14, 2013

Virginia Bioinformatics Institute (VBI), Virginia Tech

9:00 AM - 12:00 PM  Registration - VBI Lobby

12:40 - 1:00 PM  Opening Remarks and Welcome, Dr. Dennis Dean, Virginia Tech – VBI Auditorium
(all sessions held in VBI Auditorium unless otherwise noted)

Session I, Chair: Xiling Shen, Cornell University

1:00 - 1:45 PM  Arthur Lander (University of California Irvine)
The Challenges of Proliferative Control

1:45 - 2:30 PM  Thomas Pollard (Yale University)
Combining experiments and modeling to understand actin dynamics during endocytosis and cytokinesis

2:30 - 3:00 PM  Break, VBI Lobby

Session II, Chair: Will Mather, Virginia Tech

3:00 - 3:45  Rong Li (Stowers Institute)
Mechanism of cell polarization in budding yeast

3:45 - 4:05  Zhanghan Wu (National Institutes of Health)
Distinct actin networks dictate traction peak oscillation of focal adhesions

4:05 - 4:25  Ping Ye (Washington State University)
Dynamic modeling of yeast meiotic initiation

5:30 - 7:30 PM  Dinner
(Meals provided at Virginia Tech’s award winning dining hall, Dietrick Dining Hall (D2), will be served from 11am – 1:30pm and from 5 – 6:30pm. Please enjoy meals with your colleagues at D2; even after serving times, please enjoy interdisciplinary discussion until your next session begins!)
Thursday, August 15, 2013

Session III, Chair: Josep Bassaganya-Riera, Virginia Tech

9:00 - 9:45 AM  Bela Novak (University of Oxford)
               Cell cycle control by a minimal Cdk network

9:45 - 10:05 AM  Maria Davidich (Siemens)
               Examining Boolean network approach as a modeling approach
               for protein networks: Fission yeast cell cycle as an example

10:05 - 10:25 AM  Yang-Yu Liu (Harvard University)
               Observability of complex biological systems

10:25 - 10:50 AM  Break, VBI Lobby

Session IV, Chair: Abhyudai Singh, University of Delaware

10:50 - 11:40 AM  Albert Goldbeter (Universite Libre de Bruxelles)
               Regulatory networks and cellular rhythms: The cell cycle and
               the circadian clock

11:40 AM - 12:00 PM  Judit Zamborszky (University of Cincinnati)
               Circadian-gated cell division cycles in Neurospora crassa

12:00 AM - 12:10 PM  Conference Group Photo

12:10 - 2:00 PM  Lunch
               (Meals provided at Virginia Tech’s award winning dining hall,
               Dietrick Dining Hall (D2), will be served from 11am – 1:30pm
               and from 5 – 6:30pm. Please enjoy meals with your colleagues
               at D2; even after serving times, please enjoy interdisciplinary
               discussion until your next session begins!)

Session V, Chair: Alan Rendall, University of Mainz

2:10 - 2:55 PM  James Ferrell (Stanford University)
               Bistability and Trigger Waves in Mitosis

2:55 - 3:15 PM  Guang Yao (University of Arizona)
               The State of Silence

3:15 - 3:35 PM  Break, VBI Lobby
Thursday, August 15, 2013 (continued)

Session VI, Student Travel Prize Talk Session, Chair: Neil Adames, Virginia Tech

3:35 - 4:50 PM
Miriam Ginzberg (Harvard University)
*Specification of cell size and control of size heterogeneity by mTOR-dependent modulation of growth rate*

Elham Azizi (Boston University)
*Predictive Models of Gene Regulation for Mycobacterium tuberculosis*

Kai-Yuan Chen (Cornell University)
*A gradient modulated intercellular feedback controlling pattern formation inside intestinal crypts*

Phanindra Venkatapurapu (University of North Carolina)
*RGS protein Sst2 regulates receptor endocytosis in yeast*

Jaekyoung Kim
*A network design for cellular timekeeping where maintaining a fixed period is crucial*

5:00 - 8:00 PM
Poster Session (refreshments provided), VBI Lobby

Friday, August 16, 2013

Session VII, Chair: Hong Qin, Spelman College

9:00 - 9:45 AM
Tim Elston (University of North Carolina)
*Periodically probing the pheromone response of yeast*

9:45 - 10:05 AM
Chun-Chao Wang (University of Virginia)
*A dynamic expression circuit in single basal-like breast epithelial cells*

10:05 - 10:30 AM
Break, VBI Lobby
Schedule

Friday, August 16, 2013 (continued)

Session VIII, Chair: T. M. Murali, Virginia Tech

10:30 - 10:50 AM  Sayak Mukherjee (Ohio State University)
Mono- and multi-valent ligation of the BCR exhibit differential
dependence upon Syk and Src family kinases

10:50 - 11:10 AM  Sandip Kar (IIT, India)
Information flow defines code converting PI3K and MAPK
signaling to Proliferation

11:10 - 11:30 AM  Myong-Hee Sung (National Institutes of Health)
Cell type-specific processing of signaling information
by NF-xB dynamics

Session IX, Chair: John Tyson, Virginia Tech

11:30 AM - 12:30 PM  Forum for Interdisciplinary Research & Education

12:30 - 2:30 PM  Lunch
(Meals provided at Virginia Tech’s award winning dining hall,
Dietrick Dining Hall (D2), will be served from 11am – 1:30pm
and from 5 – 6:30pm. Please enjoy meals with your colleagues
at D2; even after serving times, please enjoy interdisciplinary
discussion until your next session begins!)

Session X, Chair: Xujing Wang, National Institutes of Health

2:30 - 3:15 PM  Daniela Cimini (Virginia Tech)
Defining the kinetochore mechanical properties important for
regulation of mitotic chromosome dynamics in PtK1 cell

3:15 - 3:35 PM  Steve Abel (University of Tennessee)
The Membrane Environment Can Promote or Suppress
Bistability in Cell Signaling Networks

3:35 - 3:55 PM  Break, VBI Lobby
Friday, August 16, 2013 (continued)

Session XI, Chair: Attila Csikasz-Nagy, King’s College London

3:55 - 4:40 PM  James Keener (University of Utah)  
Mechanisms of length regulation of flagella in Salmonella

4:40 - 5:00 PM  Robert Clarke (Georgetown University)  
Modeling endocrine resistance in breast cancer

5:00 - 5:05 PM  Closing Remarks

6:00 - 9:00 PM  Evening Banquet  
Inn at Virginia Tech (separate ticket purchase required, $55)

Organizing Committee

Katherine Chen, Virginia Tech  
Attila Csikasz-Nagy, King’s College London  
Christian Hong, University of Cincinnati  
William Mather, Virginia Tech  
Reinhard Laubenbacher, Virginia Tech  
Jianhua Xing, Virginia Tech
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The Challenge of Proliferative Control

Prof. LANDER, Arthur ¹

¹ University of California, Irvine

Arthur Lander¹,²,³, Kim Gokoffski¹,²,⁵, Yucheng Hu¹,⁴, Sameeren Kunche¹,³, Shimako Kawauchi¹,⁵, Peter McHale¹, Huaming Yan¹,⁴, Genti Buzi⁶, Hamed Youssefpour¹,⁴, Anne Calof¹,²,⁵, Mustafa Khammash⁶, John Lowengrub¹,⁴, and Qing Nie¹,³,⁴.

¹Center for Complex Biological Systems, and Departments of ²Developmental and Cell Biology, ³Biomedical Engineering, ⁴Mathematics, and ⁵Anatomy and Neurobiology, University of California, Irvine, and ⁶Department of Biosystems Science and Engineering, ETH-Zurich, Basel, Switzerland.

Much progress has been made over the last several decades in understanding cell proliferation at the single-cell level (e.g., cell cycle control, growth factor action). But how the proliferative behaviors of large groups of cells are collectively controlled to produce and maintain complex tissues remains poorly understood. This is surprising given the amazing feats of growth control that animals, such as ourselves, perform: we build organs and tissues of just the right size and cellular composition, maintain them within narrow tolerances and, after injury, regenerate many of them back to their original states, often very rapidly. Our lack of understanding is especially surprising given that loss of growth control is the root cause of cancer. Our group has been using both mathematical modeling and in vitro and in vivo experimentation to study proliferative dynamics and identify basic principles of tissue growth control. We find that many of the peculiar features of growing and renewing tissues—including the organization of cells into lineages, the tendency of lineages to branch, stochastic patterns of division symmetry, the use of soluble factors to provide lineage feedback, the spatial organization of cells, an emphasis on lineage progression (as opposed to cell cycle speed) as a major point of control, and even the persistence of lineage progression in cancer (the “cancer stem cell” hypothesis), can all be understood as partial solutions to the challenges of meeting a diverse and constraining set of performance objectives related, among other things, to robustness, speed, stability, and damage tolerance.
Combining experiments and modeling to understand actin dynamics during endocytosis and cytokinesis

Prof. POLLARD, Thomas

Yale University

Combining experiments and modeling to understand actin dynamics during endocytosis and cytokinesis

We combine mathematical modeling with structure determination, biochemical characterization and quantitative microscopic measurements in live cells to understand how fission yeast carry out clathrin-mediated endocytosis and cytokinesis. The proteins and mechanisms are highly conserved, so our insights are relevant to motility, endocytosis and cytokinesis of animal cells.

Arp2/3 complex mediates the assembly of branched actin filaments at sites of clathrin-mediated endocytosis. We counted the numbers of >20 fluorescent fusion proteins during the time course assembly and disassembly of endocytosis. These numbers constrain simulations of a model of the process. The mechanism is robust, and some reactions are much faster in cells than in vitro. The rapid loss of actin filaments endocytic sites involves severing by cofilin, producing short fragments that diffuse away to activate Arp2/3 complex at new sites.

Cells assemble a cytokinetic contractile ring from macromolecular complexes called nodes on the inner surface of the plasma membrane. Two types of interphase nodes come together to form cytokinesis nodes by a simple diffuse and capture mechanism. Type 2 nodes arise at new cell tips and diffuse along the membrane to the equator where they are captured by stationary Type 1 nodes. Super-resolution fluorescence microscopy of live cells has revealed the substructure of cytokinesis nodes. Transient interactions between myosin-II motors in nodes and actin filaments growing from formins in nearby nodes pull nodes into a contractile ring. Condensation of nodes into a continuous ring depends on cofilin severing the actin filaments connecting nodes. Monte Carlo simulations reliably produce anatomically realistic contractile rings in the same time as live cells and correctly predict the outcomes of experimental alterations of the reactions. After maturing for 25 min through the addition of other proteins, the contractile ring constricts to pinch the cell in two. Stochastic simulations done in collaboration with Ben O’Shaughnessy (Columbia University) have revealed how ring components spontaneously self-organize into a tension-generating bundle and how rapid turnover of these components contributes to tension generation.
Mechanism of cell polarization in budding yeast

Prof. Li, Rong

1 Stowers Institute for Medical Research

Budding yeast cells have the ability to polarize with or without the aid of spatial cues. The small GTPase Cdc42 plays a key role in orchestrating the re-organization of the actin cytoskeleton and membrane trafficking toward a specific cortical domain (referred as the polar cap). In turn, actin cable-mediated vesicular trafficking helps to localize Cdc42 to the polar cap. Early work showed that these interactions form a positive feedback loop that enables yeast cells to breaking symmetry spontaneously. Our recent study through imaging and modeling found that establishing stable cell polarity with this mechanism is critically dependent on the presence of phospholipid microdomains in the plasma membrane that restrict Cdc42 diffusion. Another mechanism for yeast symmetry breaking was proposed to require the adaptor protein Bem1, which has the ability to bind both active Cdc42 and the Cdc42 GEF Cdc24, hereby mediating a positive feedback loop achieving Cdc24 localization and Cdc42 autocatalytic activation at the site of GEF accumulation. However, recent experimental results show that Bem1 is only required for symmetry breaking when the actin polymerization is inhibited. Surprisingly, Bem1’s function in symmetry breaking does not necessitate its interaction with active Cdc42 or its own localization to the polar cap. Instead, Bem1 plays a role in boosting the level of GEF activity through direct binding to Cdc24 and this becomes critical when actin-based Cdc42 localization mechanism is disabled. A new analytical model has been constructed to account for actin-independent symmetry breaking.
Cell cycle control by a minimal Cdk network

Prof. NOVAK, Bela
Oxford University

Béla Novák, Claude Gérard, John J. Tyson and Damien Coudreuse
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In present-day eukaryotic cells, the cell division cycle is controlled by a complex network of interacting proteins, in particular members of the Cyclin and Cyclin-dependent protein kinase (Cdk) families, as well as the Anaphase Promoting Complex (APC). Successful progression through the cell cycle depends on the precise, temporally ordered regulation of the functions of these proteins. In light of this complexity, it is surprising that in fission yeast, a minimal Cdk network consisting of a single Cyclin-Cdk fusion protein is able to control DNA synthesis and mitosis in a manner that is indistinguishable from wild type cells (Coudreuse & Nurse, 2010). To improve our understanding of this minimal cell cycle regulatory network, we build, simulate and analyse a mathematical model of the molecular interactions controlling the G1/S and G2/M transitions in these minimal cells. The model accounts for all observed properties of yeast strains operating with the fusion protein system, including the unexpected fact that elimination of inhibitory phosphorylation of the Cdk module is benign in these cells while it is lethal in a wild type background. This leads us to propose a new mechanistic model explaining the phenomenon of mitotic catastrophe, relying on the combination of unregulated, multi-cyclin-dependent Cdk activity. Stochastic simulations of the model also support the conclusions drawn from the deterministic model and provide additional insights into unforeseen differences in variability of size at division in different mutant strains. The model also makes testable predictions to guide future experimental studies.

Reference:
Regulatory networks and cellular rhythms: The cell cycle and the circadian clock

Prof. GOLDBETER, Albert 1
1 Université Libre de Bruxelles

The circadian clock and the cell cycle represent examples of periodic behavior reflecting the temporal self-organization of cellular regulatory networks. Computational models of increasing complexity can be used to address the dynamics of these coupled cellular rhythms. Models throw light on the molecular mechanism of circadian rhythms and on the dynamical bases of circadian clock-related physiological disorders such as the familial advanced sleep-phase syndrome (FASPS). Modeling the mammalian circadian clock allows us to investigate its response to phase shifts of the light-dark cycle, an issue with implications for jet lag. A computational model for the network of cyclin-dependent kinases (Cdks) that controls the dynamics of the mammalian cell cycle shows that it can also display periodic behavior. A variety of factors can trigger the transition from a quiescent, stable steady state to cell proliferation driven by self-sustained oscillations in the Cdk network. The coupling of the cell cycle to the circadian clock results in the synchronization of these two major cellular rhythms.

References:


Bistability and Trigger Waves in Mitosis

Prof. FERRELL, James
1 Stanford University

Despite the large size of the Xenopus laevis egg (~1.2 mm diameter), a fertilized egg rapidly proceeds through mitosis in a spatially-coordinated fashion. Mitosis is initiated by a bistable system of regulatory proteins centered on Cdk1, raising the possibility that this spatial coordination could be achieved through trigger waves of Cdk1 activity. Using an extract system that carries out cell cycles in vitro, we show that mitosis does spread through Xenopus cytoplasm via trigger waves, propagating at a linear speed of ~60 µm/min. Perturbing the feedback loops that give rise to Cdk1’s bistability changes the speed and dynamics of the waves. Time lapse imaging of intact eggs argues that trigger waves of Cdk1 activation are responsible for surface contraction waves, ripples in the cell cortex that precede cytokinesis. These findings indicate that Cdk1 trigger waves help ensure the spatiotemporal coordination of mitosis in large eggs. Trigger waves may be an important general mechanism for coordinating biochemical events over large distances.

Periodically probing the mating response of yeast

Prof. Timothy Elston
1 The University of North Carolina

For cells to function properly they must adapt to changes in their environment often by differential regulation gene expression. The mating response pathway of Saccharomyces cerevisiae (budding yeast) has served as a useful model system for studying cell signaling. Though there have been many studies of this pathway, a predictive mathematical model of this system is still lacking. In this study, we combine a novel short-lived fluorescent reporter (~ 7min half-life) with a microfluidics device that allows dynamic control pheromone concentrations to perform a frequency response analysis of the pheromone signaling pathway. This analysis allowed us to develop a mathematical model of transcriptional regulation capable of predicting the systems response to genetic perturbations.
Defining the kinetochore mechanical properties important for regulation of mitotic chromosome dynamics in PtK1 cell

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In PtK1 cells, metaphase chromosomes display specific dynamic behavior, with the chromosomes in the middle of the metaphase plate exhibiting regular oscillations, and the peripheral chromosomes not oscillating. We recently developed a mathematical model to investigate this phenomenon and found that it can be explained by: (i) non-motor viscoelastic linkages between kinetochores and microtubules, which we propose being mediated by the Hec1 subunit of the Ndc80 complex; and (ii) differences in the distribution of polar ejection forces along the metaphase plate. Thus, we intended to study the mechanical properties of Hec1 to test whether it does, indeed, behave as a viscoelastic component of the kinetochore-microtubule interface. To this end, we used an experimental protocol that allowed us to first induce kinetochore stretching in live PtK1 cells with fluorescently labeled Hec1, then release the stretching by severing kinetochore-bound microtubules using laser microsurgery, and finally follow by confocal microscopy and quantify the decrease in stretching/size of Hec1 after release of the pulling forces on the kinetochore. Using this approach, we found that the vast majority of stretched kinetochores displayed a response typical of viscoelastic materials, with an initial rapid reduction in stretching/size, followed by a period of much slower change in size. This finding supports our mathematical model’s central assumption that the kinetochore-microtubule linkages (i.e., Hec1) are viscoelastic. This may be important for maintaining dynamic kinetochore-microtubule interactions in metaphase and for correction of kinetochore-microtubule mis-attachments, thus contributing to accurate chromosome segregation.
Mechanisms of length regulation of flagella in Salmonella

Prof. KEENER, James

1University of Utah

The construction of flagellar motors in motile bacteria such as Salmonella is a carefully regulated genetic process. Among the structures that are built are the hook and the filament. The length of the hook is tightly controlled while the length of filaments is less so. However, if a filament is broken off it will regrow, while a broken hook will not regrow. The question that will be addressed in this talk is how Salmonella detects and regulates the length of these structures. This is related to the more general question of how physical properties (such as size or length) can be detected by chemical signals and what those mechanisms are.

In this talk, I will present mathematical models for the regulation of hook and filament length. The model for hook length regulation is based on the hypothesis that the hook length is determined by the rate of secretion of the length regulatory molecule FliK and a cleavage reaction with the gatekeeper molecule FlhB. A stochastic model for this interaction is built and analyzed, showing excellent agreement with hook length data. The model for filament length regulation is based on the hypothesis that the growth of filaments is diffusion limited and is measured by negative feedback involving the regulatory protein FlgM. Thus, the model includes diffusion on a one-dimensional domain with a moving boundary, coupled with a negative feedback chemical network. The model shows excellent qualitative agreement with data, although there are some interesting unresolved issues related to the quantitative results.
Examining Boolean network approach as a modelling approach for protein networks: Fission yeast cell cycle as an example

Dr. DAVIDICH, Maria
1 Siemens AG/Bremen university

Boolean network approach is becoming more and more popular as a coarse-grained approach for modelling of gene and protein networks. The natural question is whether Boolean network-based models are also suitable for predicting the evolution of biological process in the presence of mutations.

We examine the predictability power of Boolean network models using the fission yeast cell cycle as an example. We construct such a model based on known biochemical reactions and examine how the approach works for wild-type cell cycle and mutations. Our results show that the said Boolean network model of a fission yeast cell cycle is able to predict not only the wild-type pattern of protein activations, but also a large number (32) of single, double and triple mutations, some of which have not been modelled before.

The results obtained suggest that Boolean network models cover the regulatory mechanisms better than it has been assumed so far due to the rather robust nature of regulatory networks.
Observability of complex biological systems

Dr. LIU, Yang-Yu 1; Prof. SLOTINE, Jean-Jacques 2; Prof. BARABÁSI, Albert-László 3

1Brigham and Women’s Hospital and Harvard Medical School
2Massachusetts Institute of Technology
3Northeastern University and Harvard Medical School

A quantitative description of a complex system is inherently limited by our ability to estimate the system’s internal state from experimentally accessible outputs. Although the simultaneous measurement of all internal variables, like all metabolite concentrations in a cell, offers a complete description of a system’s state, in practice experimental access is limited to only a subset of variables, or sensors. A system is called observable if we can reconstruct the system’s complete internal state from its outputs. Here, we adopt a graphical approach derived from the dynamical laws that govern a system to determine the sensors that are necessary to reconstruct the full internal state of a complex system. We apply this approach to biochemical reaction systems, finding that the identified sensors are not only necessary but also sufficient for observability. The developed approach can also identify the optimal sensors for target or partial observability, helping us reconstruct selected state variables from appropriately chosen outputs, a prerequisite for optimal biomarker design. Given the fundamental role observability plays in complex systems, these results offer avenues to systematically explore the dynamics of a wide range of natural, technological and socioeconomic systems.
Circadian-gated cell division cycles in Neurospora crassa

Dr. HONG, Christian I; Dr. ZAMBORSZKY, Judit; J. BELDEN, William; Dr. CSIKASZ-NAGY, Attila; BAEK, Mokryun; Dr. LABISCSAK, Laszlo; JU, Kyungsu; LEE, Hyeyeong; Dr. LARRONDO, Luis F.; GOITY, Alejandra; SIONG CHONG, Hin

1University of Cincinnati, College of Medicine
2University of Cincinnati College of Medicine
3The State University of New Jersey, Department of Biochemistry and Microbiology
4Research and Innovation Center, Fondazione Edmund Mach
5Department of Molecular Biology and Physiology, University of Cincinnati
6Departamento de Genética Molecular y Microbiología, Facultad de Ciencias Biológicas

Asynchronous nuclear divisions are readily observed in filamentous fungi such as Ashbya gossypii and Neurospora crassa. Our computational simulations, however, predict synchronous circadian clock-gated mitotic divisions if the division cycles of such multinucleated organisms are coupled with circadian rhythms. Based on this hypothesis, we investigate the coupling between the cell cycle and the circadian clock in Neurospora crassa. First, we show WC-1-dependent light-induced expression of stk-29 mRNA (homolog of wee1), which suggests that there exists a conserved coupling between the clock and the cell cycle via STK-29 in Neurospora as in mammals. Second, we demonstrate that G1 and G2 cyclins, CLN-1 and CLB-1, respectively, show circadian oscillations with luciferase bioluminescence reporters. Moreover, clb-1 and stk-29 gene expressions show circadian clock-dependent light-induced phase shifts, which may alter the timing of divisions. Third, we show circadian clock-dependent synchronized nuclear divisions by tracking nuclear morphology with histone hH1-GFP reporter. Synchronized divisions occur late in the evening, and they are abolished in the absence of circadian rhythms (frqKO). Our findings demonstrate the importance of circadian rhythms for synchronized mitotic cycles and establish Neurospora crassa as an ideal model system to investigate mechanisms that couple the cell cycle and the circadian clock.
The State of Silence

Dr. YAO, Guang 1; Dr. MITCHELL, Geoff 1
1 Univ. of Arizona

Most cells in our body are “silent”, at the so called quiescent state. Quiescent cells are non-dividing and they enter cell proliferation only in the presence of specific growth signals. Proper control of cellular quiescence is fundamental to tissue homeostasis; disruption of this control can lead to a wide range of diseases including cancer, fibrosis, autoimmune disease, and aging. Despite its importance, the basic molecular mechanism underlying cellular quiescence remains elusive. By coupling modeling and experiments, we have recently demonstrated that the Rb-E2F gene network functions as a bistable switch; the Rb-E2F bistable switch converts graded and transient serum growth signals into a binary and hysteretic E2F activation, which drives cell proliferation. We now further show that the Rb-E2F bistable switch functions robustly under different quiescent conditions (e.g., serum starvation, cell contact inhibition), and the Off-state of the Rb-E2F bistable switch defines cellular quiescence. Interestingly, we found that the Off-state of the Rb-E2F switch has different “depths”; deeper quiescent states are characterized by lower likelihoods to switch On the Rb-E2F bistable switch and proliferate. Controlling the switching dynamics of the Rb-E2F bistable switch may hold the promise to re-establish normal quiescent states in a variety of hyper- and hypo-proliferative diseases.
A dynamic expression circuit in single basal-like breast epithelial cells

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Basal-like carcinoma is a subtype of breast cancer that is characterized by poor prognosis and high intratumor heterogeneity. In basal-like breast epithelia, we have identified two anticorrelated gene-expression programs that arise among single extracellular matrix (ECM)-attached cells during organotypic 3D culture. The first program contains multiple TGFβ-related genes including TGFBR3, and its heterogeneous induction is critical to suppress ductal branching. The second program contains JUND together with the basal-like marker, KRT5. Homogenizing JUND expression in single cells leads to 3D acini with bridged lumina that are similar to cribriform ductal carcinoma in situ. TGFBR3 and JUND together comprise a circuit that is interconnected via four negative-feedback loops. Computational modeling of the circuit predicts damped, antiphase oscillations upon stimulation with endogenous impulses of TGFβ-like ligand, and we directly observe these spontaneous responses in 3D culture by live-cell imaging. The TGFBR3–JUND circuit is remarkably conserved in early basal-like tumors that heterogeneously express KRT5, suggesting that asynchronous circuit dynamics are active in this patient subset. We further show that the circuit is strongly dependent on ECM engagement, as detachment leads to a rewiring that is triggered by RPS6 dephosphorylation and maintained by juxtacrine signaling from tenascin C. Breast tumor heterogeneity need not stem from partial basal-like differentiation and could instead reflect dynamic toggling of individual cells between expression states.
Mono- and multi-valent ligation of the BCR exhibit differential dependence upon Syk and Src family kinases

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Two distinct sets of kinases (the Src family and Syk) play critical roles in initiating membrane-proximal B cell receptor (BCR) signaling. However, unlike in other lymphocytes such as T cells, the “division of labor” between Src family kinases (SFKs) and Syk in B cells is not well separated, because Syk can also phosphorylate immunoreceptor tyrosine-based activation motifs (ITAMs), a primary substrate for SFKs. Why do B cells require SFKs in addition to Syk for activation? We investigated the role of both families of kinases in BCR signaling using computational modeling and in vitro experiments. We found that recombinant Syk, unlike the related kinase ζ-associate protein of 70 kilodaltons (Zap70), mediated ITAM phosphorylation in the absence of SFKs. Our computational model suggests that positive feedback enables Syk to substantially compensate for the absence of SFKs when spatial clustering in BCRs is induced by multimeric ligands. We confirmed this prediction experimentally. In contrast, when B cells were stimulated by monomeric ligands that fail to produce BCR clustering, both Syk and SFKs were required for robust BCR activation. Our data suggest that SFKs could play a pivotal role in increasing BCR sensitivity to monomeric antigens of pathogens and for mediating a rapid response to soluble multimeric antigens of pathogens that can induce spatial BCR clustering.
Information flow defines code converting PI3K and MAPK signaling to Proliferation

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Akt and ERK, are the central regulators of cell growth and proliferation in mammalian cells. Growth factors commonly activate Akt and ERK through the phosphoinositide 3 kinase (PI3K)/Akt and MAP-kinase signaling pathway respectively but downstream effects can be cell-type specific. To gain a quantitative understanding of how these pathways collectively control cell fate, we studied them in two murine hematopoietic cell types that strictly depend on the growth factor erythropoietin (Epo): erythrocyte progenitors, CFU-E cells, and the lymphoid cell line BaF3-EpoR. Experimentally, we found qualitatively different dynamic responses to stimulation with Epo in the two cells. Transient activation of the Epo receptor in CFU-E cells triggered sustained, high-amplitude Akt activity, whereas Akt activation in BaF3-EpoR cells remained comparatively weak and transient despite prolonged Epo receptor activity. On the contrary, ERK activation seems quite similar in both the cell type. We developed a dynamical model of the underlying molecular interaction network and showed that the distinct behavior of the two cell types is explained by different expression levels of PI3K/Akt and MAP-kinase pathway components. Statistical analysis of the pathway inhibitor data further predicts that the proliferation in CFU-E cells is more PI3K/Akt pathway dependent whereas BaF3-EpoR cells depend on both pathways for proliferation. Using the simple metric of ‘integrated response’ we were able to verify this prediction with the already developed dynamical model for both the cell type. Taken together, our results outline a combined modeling and experimental strategy to dissect the cell type-specific dynamics and functioning of signal transduction pathway.
Cell type-specific processing of signaling information by NF-κB dynamics

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1 NIH

Live cell imaging, genome-wide assays, and mathematical modeling provide key insights in the systems cell biology of transcription factor signaling. NF-κB, a key transcriptional regulator of immunity and cell survival, operates within a complex regulatory network. Theoretical considerations lead to the possibility of stimulus-induced oscillations in the network with multiple ‘waves’ of NF-κB accumulation in the nucleus. Our study of the real time dynamics of NF-κB in living cells using GFP knock-in mouse fibroblasts is an experimental validation of such oscillations in a physiological system. The nuclear level of NF-κB oscillates asynchronously up to several cycles in response to TNF-κ. We also discovered different aspects of NF-κB dynamics acting on multiple timescales, by custom-tailed quantitative live cell microscopy techniques. Mathematical modeling suggests that negative feedback loops do not simply terminate signaling, but rather promote NF-κB oscillations possibly for a functional advantage. Single fibroblasts respond to a range of TNF-κ concentrations in a digital all-or-none fashion. More recently, we have uncovered a distinct principle of NF-κB signaling by examining macrophages responding to bacterial stimuli. In this immune cell type, the NF-κB network is re-wired by a novel positive feedback mechanism for analog signal processing and phenotype-switching to a fully active anti-bacterial response. These results suggest that the same transcription factor may interpret and process signaling information in a digital or analog manner depending on the functional need imposed upon the cell type.
The Membrane Environment Can Promote or Suppress Bistability in Cell Signaling Networks

Prof. ABEL, Steven

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Many key biochemical reactions that mediate signal transduction in cells occur at the cell membrane, yet how the two-dimensional membrane environment influences the collective behavior of many signaling networks is poorly understood. In an effort to gain insight into the role of the membrane in signal transduction, we use computational methods that explicitly account for stochastic fluctuations to study two topologically different signaling pathways that exhibit bistability: the distributive enzymatic modification of a protein at multiple sites and the positive feedback-mediated activation of a protein. The choice of these networks is motivated by membrane-proximal signaling events in T cells, which act as cellular detectors of pathogens and orchestrate adaptive immunity. In both networks we find that confining proteins to a membrane-like environment can markedly alter the emergent dynamics. The signaling motifs are influenced by membrane features including reduced protein mobility, increased protein concentration, and altered spatiotemporal correlations between pairs of enzyme and substrate molecules. For the distributive protein modification network, increased protein concentration promotes bistability, while lower mobility and membrane-enhanced spatiotemporal correlations suppress bistability. For the positive feedback-mediated activation network, confinement to a membrane environment enhances protein activation, and spatially localized concentration fluctuations can result in the formation and growth of regions with high concentrations of active proteins. By comparing the behavior of the two networks, it is seen that the influence of the membrane on signaling can be qualitatively different for signaling motifs with different network topologies.
Modeling endocrine resistance in breast cancer

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70% of all newly diagnosed invasive breast cancers express the molecular target estrogen receptor-alpha (ER). Target therapies include antiestrogens that compete with 17β-estradiol for binding to ER and aromatase inhibitors that block the production of E2 in the body. While these drugs can reduce the 10-year risk of cancer recurrence and death by about one-third, overall almost 50% of patients with ER+ breast cancer will ultimately experience a recurrence of their disease. Our lack of understanding the precise mechanisms driving resistance/recurrence represents a major barrier to progress in the field. While much is known about the function of ER, its ability to regulate the transcription of many genes, some of which themselves are also transcription factors, creates complex signaling with considerable noise. The formidable challenge of attempting to understand such signaling, and how it controls responsiveness to endocrine therapies, requires in silico modeling. We began by constructing a general modular roadmap to guide our studies of ER-regulated signaling, with the explicit goal of eventually understanding the switches and control mechanisms that affect several cell functions (modules) including cell cycle, apoptosis, autophagy, and cellular metabolism. By focusing on functionally important modules, the models use data strongly linked to key mechanistic actions within cells. Currently, using novel bioinformatics tools on our own genome-wide data sets, we have obtained new insights into the signaling networks of breast cancer cells. Using information gleaned from these studies and our existing knowledge of system function, we have begun to use experimental studies focused on specific aspects of the signaling network to build precise mathematical models that help us to understand biological outcomes in terms of underlying molecular mechanisms. The integration of bioinformatics analysis and mathematical modeling with experimental data generates new hypotheses and guides subsequent experimental design. The multidisciplinary approach is a powerful method for studying the signaling modules that control and execute complex biological functions in normal and cancer cells. We will present some of these models and an overview of what we have learned about cell fate outcomes in response to antiestrogen treatment.
Dynamic modeling of yeast meiotic initiation

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Meiosis is the sexual reproduction process common to eukaryotes. The diploid yeast Saccharomyces cerevisiae undergoes meiosis in sporulation medium to form four haploid spores. Initiation of the process is tightly controlled by intricate networks of positive and negative feedback loops. Intriguingly, expression of early meiotic proteins occurs within a narrow time window. Further, sporulation efficiency is strikingly different for yeast strains with distinct mutations or genetic backgrounds. To investigate signal transduction pathways that regulate transient protein expression and sporulation efficiency, we develop a mathematical model using ordinary differential equations. The mathematical model is capable of simulating the orderly and transient dynamics of meiotic proteins including Ime1, the master regulator of meiotic initiation, and Ime2, a kinase encoded by an early gene. The model is validated by quantitative sporulation phenotypes of single-gene knockouts. Thus, we can use the model to make novel predictions on the cooperation between proteins in the signaling pathway. Virtual perturbations on feedback loops suggest that both positive and negative feedback loops are required to terminate expression of early meiotic proteins. Bifurcation analyses on feedback loops indicate that multiple feedback loops are coordinated to modulate sporulation efficiency. In particular, positive auto-regulation of Ime2 produces a bistable system with a normal meiotic state and a more efficient meiotic state. In summary, our mathematical model uncovers key regulations that can be manipulated to enhance sporulation efficiency, an important first step in the development of new strategies for producing gametes with high quality and quantity.
Specification of cell size and control of size heterogeneity by mTOR-dependent modulation of growth rate

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The homogeneity in cell size observed in normal proliferating tissues, and the contrasting heterogeneity characteristic of several cancers, suggest that control mechanisms coordinate growth and cell cycle progression. We used quantitative fluorescence microscopy to measure cell cycle position, total protein content, and the levels of several cell growth regulators in tandem in single cells. Analysis of the joint distribution of cell size and cell cycle position in a population revealed a control mechanism that restricts cells to a specified size range at several points in the cell cycle. Combining our measurements with live-cell imaging showed that this restriction is the result of a negative correlation between growth rate and cell size, indicating that cells sense their own size and modulate their growth accordingly. We also observed cell-size-dependent adjustments of cell cycle length, which further reduced size variability. We then identified drugs that change the mean cell size without disrupting the cell-autonomous control mechanism, as well as drugs that weaken the size-dependence of either growth rate or cell cycle progression. In particular, mTOR inhibition decouples the rate of cell growth from cell size, impairing the efficiency of cell size specification and increasing size variability. This effect is strongest during S-phase, consistent with our measurements of mTOR activity as a function of size and cell cycle position which suggest that mTOR assumes its role in growth control following S-phase entry. These results demonstrate that the mTOR pathway maintains size homogeneity by stimulating growth in a cell-size-dependent manner after G1 exit.
Predictive Models of Gene Regulation for Mycobacterium tuberculosis

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We have generated the first genome scale model of the M. tuberculosis regulatory network and combined this network with the first comprehensive profiling of mRNA, proteins, metabolites and lipids in MTB during hypoxia and re-aeration [1]. Adaptations to hypoxia and metabolic alterations such as switching to catabolism of host lipids are thought to play a prominent role in MTB pathogenesis. To date, we have mapped regulatory bindings of more than 100 Transcription Factors (TFs) in MTB through a high-throughput system based on ChIP-Seq. We have developed computational predictive models of gene expression by integrating this network with transcriptomics data obtained from the induction of the same factors. Our regulatory models are able to predict gene expression in hypoxic conditions as well as expressions in knock-outs of particular regulators. We also extend these models in the context of module networks to predict combinatorial regulations. In order to identify the key factors contributing to metabolic alterations, we have also coupled regulatory and metabolic models, to translate the predicted impacts of TF perturbations to the level of metabolite productions.

Reference:
A gradient modulated intercellular feedback controlling pattern formation inside intestinal crypts

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The small intestine and colon are lined with a single layer of epithelial cells. The epithelium is full of crypts, which are invaginations into the underlying connective tissue. The intestinal epithelium is replaced every 3-5 days, making it the fastest regenerative tissue in the body. To maintain homeostasis, stem cells are tightly controlled by a niche at the bottom of the crypt. Inside the niche, 12–14 Lgr5+ stem cells form soccer-ball-like pattern with CD24+ Paneth (niche) cells. Divided cells leave the niche and migrate up while differentiating into absorptive (enterocyte) and secretory (Goblet) lineages, eventually forming more random cell fate patterns at the top. However, it remains unclear how local cell interaction mechanisms give rise to the diverse patterns at different crypt locations.

Notch signaling depends on ligands on a cell activating receptors on a neighboring cell. Stem cells and enterocytes express high levels of Notch receptors while Paneth and Goblet cells express high levels of Notch ligands, suggesting that Notch plays a role in pattern formation.

We first built an intercellular Notch signaling model based on transcriptional feedback. Even though the model can generate individual patterns, it is not capable of replicating the spatially varying patterns inside the crypt.

We then investigated an alternative mechanism, in which activated Notch receptors form a positive feedback by upregulating their own expression while receptors and ligands mutually inactivate each other in the same cell. Coupled with a paracrine Wnt gradient, this model faithfully replicated the spatially varying crypt patterns.

We experimentally tested whether such a mechanism exists in intestinal cells. RT-pPCR and western blots confirmed the expected upregulation of Notch receptors and downregulation of Notch ligands after addition of recombinant Notch ligands to 3D intestinal organoid culture. Immunohistochemistry on cryosectioned mouse intestinal crypts further confirmed the model predictions.

Last, we asked the question why evolution has favored this alternative mechanism over transcriptional feedback. Computational analysis revealed that this alternative mechanism generates more robust patterns in a more speedy fashion, which is important for maintaining homeostasis during the rapid turnover of the intestinal epithelium.
RGS protein Sst2 regulates receptor endocytosis in yeast

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G-protein coupled receptor (GPCR) signaling is fundamental to various processes such as cardiac contractility, immune response and gradient sensing. Budding yeast, Saccharomyces cerevisiae detect gradients of pheromone as low as 1-5% across their diameter and generate appropriate morphological response. Ste2, a GPCR, acts as a sensor for extra-cellular pheromone and initiates mating in yeast. Polarization of Ste2 has been implicated in pheromone gradient sensing. Recent work has suggested that endocytosis is important in establishing polarity of membrane proteins but the precise mechanism by which Ste2 endocytosis generates a polarized Ste2 distribution is not yet known. We speculate that differential endocytosis of receptors can establish receptor polarity. Regulator of G-protein Signaling (RGS) protein, Sst2 negatively regulates G-protein activity and facilitates mating pathway desensitization in yeast. Preliminary data from our lab suggests that Sst2 has a positive affect on gradient sensing, as sst2Δ mutants are defective in tracking pheromone gradients. Here we provide evidence suggesting that Sst2, which interacts with Ste2 using its DEP domains, blocks Ste2 endocytosis. A weak initial polarization of Ste2, generated either spontaneously or by an external gradient, is amplified by Sst2-mediated blocking of Ste2 endocytosis, thereby, generating a polarized receptor distribution, thus achieving better gradient sensing.
A network design for cellular timekeeping where maintaining a fixed period is crucial

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A negative feedback loop with a fast additional positive feedback loop has been proposed as a robust design of biological oscillator, which generating rhythms for a wide range of parameters. However, the periods of rhythms generated by this structure varies widely for parameter changes. This indicates that the structure is not appropriate for biological oscillators, in which maintaining a constant period is crucial like the circadian clocks. Interestingly, by studying the circadian clocks, we found that an opposite structure is robust for both rhythm generation and period: a negative feedback loop with a slow additional negative feedback loop. Furthermore, this structure becomes robust when the core negative feedback loop functions through a universal motif of circadian timekeeping, where repressors bind activators rather than directly binding to DNA instead of a traditional motif used in most previous model (Hill-type equation). All of these results are validated by 1) the simulation of the detailed model of mammalian circadian clock, the Drosophila clock model and the simple and general model of circadian clocks, 2) local and global stability analysis and 3) experimental data. Our study proposed a novel design for the biological oscillator, which allows the tight regulation of period.
Abstracts – Posters

Poster number (submission number)
Poster 1 (23)

Coupled Reversible and Irreversible Bistable Switches Underlying TGFß induced Epithelial to Mesenchymal Transition

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Epithelial to mesenchymal transition (EMT) plays important roles in embryonic development, tissue regeneration and cancer metastasis. While several feedback loops have been shown to regulate EMT, it remains elusive how they coordinately modulate EMT response to TGF-ß treatment. We construct a mathematical model for the core regulatory network controlling TGF-ß-induced EMT. Through deterministic analyses and stochastic simulations, we show that EMT is a sequential two-step program that an epithelial cell first transits to partial EMT then to the mesenchymal state, depending on the strength and duration of TGF-ß stimulation. Mechanistically the system is governed by coupled reversible and irreversible bistable switches. The SNAIL1/miR-34 double negative feedback loop is responsible for the reversible switch and regulates the initiation of EMT, while the ZEB/miR-200 feedback loop is accountable for the irreversible switch and controls the establishment of the mesenchymal state. Furthermore, an autocrine TGF-ß/miR-200 feedback loop makes the second switch irreversible, modulating the maintenance of EMT. We provide a mechanistic explanation on multiple experimental observations. We are using MCF-10A cell line to verify these predictions. Preliminary excremental results validate the two-phase dynamics of EMT. Other predictions, such as hysteretic dynamic behaviors, system response to pulsed stimulation and various perturbations, are under test. These results will quantitatively confirm the mathematical model and provide a systems-level understanding of TGF-ß-induced EMT.
Abstracts – Posters

Poster 2 (0)
A model of nuclear organization reveals new chromosome regions with significant affinity for the nuclear envelope

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We describe a method for modeling the three dimensional (3D) organization of the interphase nucleus, and its application to polytene chromosomes of Drosophila melanogaster salivary glands. The model represents chromosomes as polymer chains confined within the nucleus. Physical parameters of the model are taken directly from experiment, no fitting parameters are introduced. The model is used to simulate chromosome tracing data and identify the statistically significant chromosome-nuclear envelope (Chr-NE) contacts in experimental chromosome tracing data. Using this approach, 33 new Chr-NE contacts are revealed. Most of these new Chr-NE contacts correspond to intercalary heterochromatin – gene poor, dark staining, late replicating regions of the genome; only three correspond to euchromatin – gene rich, light staining, early replicating regions of the genome. Analysis of regions least likely to form Chr-NE contacts reveals that these are mostly euchromatic, but may contain late replication regions or intercalary heterochromatin. These results reveal new details about the types of chromatin likely to form Chr-NE contacts. In addition, methods are developed to objectively quantify chromosome territories and intertwining, these are discussed in the context of the corresponding experimental observations.
A numerical procedure for model reduction using the generalized Langevin equation formalism

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The Zwanzig-Mori projection formalism is widely used in studying systems with many degrees of freedom. Recently Xing and Kim used the projection formalism and derived the generalized Langevin equations (GLEs) for a general stochastic system not necessarily obeying detailed balance. In this study we develop a numerical procedure to reconstruct the GLEs from data. Numerical tests on two biological networks show remarkable agreement between the results calculated from the reconstructed GLEs and those of full model simulations. We suggest that the procedure can be applied in model reduction and a novel way of nonlinear time series analysis.
Coupled two-layer Potts model explains collective epigenetic histone modification dynamics

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Cells sharing the same set of genomes may exist in different and inheritable cell fates. Epigenetic histone covalent modification is one of the main mechanisms regulating this non-genetic inheritance.

However, the exact molecular mechanism for epigenetic memory is not clear. Using experimentally observed molecular properties and estimated parameters, we construct a discrete-state Potts model describing the dynamics of a linear chain of nucleosomes, formed by histones wrapped with DNA, with both their binding states of histone modification enzymes, and their covalent modification states. Changing of the binding states, which is often in subsecond time scales, is treated as an equilibrium process and can be represented by transfer matrices. Our stochastic simulations and analysis reveal that cooperative enzyme binding leads to effective nonlocal influence of a nucleosome on the covalent state of others; this nonlocal cooperative effect, together with a positive feedback caused by nucleosome covalent state dependent enzyme binding affinity, allow a nucleosome to "read" the covalent state of others, and "write" on itself a covalent state biased to the majority of others. The resultant epigenetic histone modification patterns are robustly inheritable against strong perturbations due to stochastic enzymatic reactions, histone turnovers, and cell cycle dependent histone replacements.
Poster 5 (45)

Systematic Reverse Engineering Approach for Searching Network Topologies: Application to Resettable Bistable Cellular Responses

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A focused theme in systems biology is to uncover the design principles of biological networks. For this purpose we develop a genetic reverse engineering procedure and a computer package to exhaustively enumerate network topologies with a fixed number of nodes that exhibit a given dynamic behavior. That is, we searched the full continuous parameter space associated with the governing dynamic equations without pre-assuming the nature of interactions between the nodes. We test the method on a previously studied problem, identifying three-node networks leading to resettable bistable behavior, which has been developed to analyze the mammalian cell quiescence-to-proliferation Rb-E2F regulatory network. We identify the minimal topology for generating resettable bistability in a systematic way and analyze associated properties of pathway cross-talks. The topology, which is responsible for generating resettable bistability, is consistent with what reported previously, indicating the effectiveness of the present approach. This general approach is readily applicable to systems with larger number of nodes.

Key References:


Poster 6 (81)

From continuous epigenetic landscapes to discrete state networks approaches describing cell phenotypic transitions

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Recent breakthroughs of cell phenotype reprogramming impose theoretical challenge on unravelling the complexity of large circuits maintaining cell phenotypes coupled at many different epigenetic and gene regulation levels, and quantitatively describing the phenotypic transition dynamics. A popular picture proposed by Waddington views cell differentiation as a ball sliding down a landscape with valleys corresponding to different cell types separated by ridges. Based on theories of dynamical systems we establish a novel “epigenetic state network” framework that captures the global architecture of cell phenotypes, which allows us to translate the metaphorical low-dimensional Waddington’s epigenetic landscape concept into a simple-yet-predictive rigorous mathematical framework of cell phenotypic transitions. Specifically, we simplify a high dimensional epigenetic landscape into a collection of discrete states corresponding to stable cell phenotypes connected by optimal transition pathways among them. We then apply the approach to the reprogramming process of fibroblasts to induced pluripotent stem cells (iPSC) and cardiomyocytes. The epigenetic state network for this case predicts three major pathways of reprogramming. One pathway goes by way of induced pluripotent stem cells (iPSC) and continues on to the normal pathway of cardiomyocyte differentiation. The other two pathways involve transdifferentiation (TD) either indirectly through cardiac progenitor (CP) cells or directly from fibroblast to cardiomyocyte. The predicted pathways and multiple intermediate states are supported by existing microarray data and other experiments. Our approach provides a theoretical framework for studying cell phenotypic transitions. Future studies at single cell levels can directly test the model predictions.
Poster 7 (92)

Bacteria know physics, well!

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Physicists like to construct simple theories, while biology is regarded as hopelessly complex. Here I summarize a series of work on the bacterial flagellar motor (BFM) with my collaborators to show that simply physics often underlies a complex biological phenomenon.

BFMs are ion-driven rotatory motors push bacteria to swim around. Experimental measurement on the motor torque-speed relations show that a BFM can function close to thermodynamic limit up to several hundred Hertz, then the motor torque drops quickly with increasing speed. Our analysis (Xing et al. PNAS 2006) shows that this long time puzzling behavior is a simple manifestation of the second law of thermodynamics. The model also predicts performance of the motor as a multi-cylinder engine deteriorate quickly as different parts are out of phase at high speed. However, subsequent experiments reveal it is not so severe. Further model studies (Bai et al. Biophys J 2009) show that bacteria use simple elastic buffering components to solve this engineering challenge. Finally we show (Bai et al. Phys Rev Lett 2012) how simple time scale arguments explain the peculiar coupling between torque-generation and motor switch. The latter may allow bacteria to explore their physical environments and response accordingly.
Conditions for invasion of synapse-forming HIV variants

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University of Delaware

Infection by Human Immunodeficiency Virus is a widespread cause of progressive immunodeficiency and death. The mechanisms of virus transmission and infection are well-documented from many experimental studies. These show that the infection of CD4+ T Cells by HIV happens by two distinct mechanisms: cell-free transmission by free viruses, and cell-cell transmission in which viral particles are transmitted directly across a tight junction or synapse between an infected and an uninfected cell. In this paper, a mathematical model of HIV transmission including both the cell-free and cell-cell transmission pathways is introduced. A variation of this model is considered including two populations of virus. The first infects cells only by the cell-free virus pathway, and the second infects cells by either the cell-free or the cell-cell pathway. Steady-state and bifurcation analyses are performed on this model. A simple formula is presented describing the bifurcation point for local stability of a steady-state solution consisting entirely of the first viral subtype. This is equivalent to the conditions for invasion by a synapse-forming HIV variant. Synapse-forming HIV is shown to provide an evolutionary advantage relative to non synapse-forming virus when the average number of virus transmitted across a synapse is a sufficiently small fraction of the burst size. The exact bifurcation point depends on the fitness of the non synapse-forming virus and the likelihood of successful infection as a function of multiplicity of infection. These results are important for understanding synaptic transmission in HIV, which has been identified as a possible cause of continued replication during antiviral therapy.
Poster 9 (4)
Modeling partitioning in cell division and subsequent aging in Bacteria

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One important event of the cell cycle is the stochastic partitioning of sub-cellular components between daughter cells in division. We explore in silico how this process affects the kinetics of cellular regulatory networks and, subsequently, the phenotypic diversity of cell populations. For this, we propose a stochastic model cell division and molecule partitioning, along with a model of gene expression within each cell, and use it to study the effects of different molecule partitioning schemes on the cell-to-cell diversity of populations. The partitioning schemes differ in the amount of added variance after partitioning of proteins in division.

First, we show that the distributions of protein levels in the population differ for different partitioning schemes. Next, we model the formation of protein aggregates and investigate the effects of different partitioning schemes for these aggregates on the aging process of the cells. We find that highly variable (i.e. asymmetric) partitioning schemes increase the overall vitality of the population. Our results provide support for the evolutionary benefits of the segregation of damage at the expense of a sub-population of aging individuals.
Dynamical Scenarios for Chromosome Bi-orientation

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Chromosome bi-orientation at the metaphase spindle is essential for precise segregation of the genetic material. The process is error-prone, and error-correction mechanisms exist to switch misaligned chromosomes to the correct, bi-oriented configuration. Here, we analyse several possible dynamical scenarios to explore how cells might achieve correct bi-orientation in an efficient and robust manner. We first illustrate that tension-mediated feedback between the sister kinetochores can give rise to a bi-stable switch, which allows robust distinction between a loose attachment with low tension, and a strong attachment with high tension. However, this mechanism has difficulties in explaining how bi-orientation is initiated starting from unattached kinetochores. We propose four possible mechanisms to overcome this problem, and assess their impact on the bi-orientation process. Based on our results and supported by experimental data, we put forward two elegant mechanisms with the potential to promote bi-orientation both efficiently and robustly.
Viscoelastic bonds and differences in polar ejection forces control kinetochore dynamics in PtK1 cells

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Duplicated mitotic chromosomes aligned at the metaphase plate maintain dynamic attachments to spindle microtubules via their kinetochores, and multiple motor and non-motor proteins cooperate to regulate their behavior. Depending on the system, sister chromatids may display either of two distinct behaviors, namely (i) the presence or (ii) the absence of oscillations about the metaphase plate. Significantly, in PtK1 cells, both types of behavior are observed within the same spindle, but how and why these distinct behaviors are manifested is unclear. Here, we developed a new quantitative model to describe metaphase sister kinetochore dynamics via kinetochore-microtubule interactions mediated by non-motor viscoelastic linkages. Our model reproduces all the key features of metaphase sister kinetochore dynamics in PtK1 cells, and suggests that differences in the distribution of polar ejection forces at the periphery and in the middle of PtK1 cell spindles underlie the observed dichotomy of chromosome behavior.
Why would a genotypically homozygous population of cells live to different ages? To address this question, I propose a mathematical model of cellular aging based on gene interaction network. This model network is made of only non-aging components, and interactions among genes are inherently stochastic. Death of a cell occurs in the model when an essential gene loses all of its interactions. The key characteristic of aging, the exponential increase of mortality rate over time, can arise from this model network with non-aging components. Hence, cellular aging is an emergent property of this model network. The model predicts that the rate of aging, defined by the Gompertz coefficient, is proportional to the average number of interactions per gene and that stochastic heterogeneity is an important factor in shaping the dynamics of the aging process. Preliminary experimental results to test the model predictions will then be presented.
Abstracts – Posters

Poster 13 (20)
Mathematical modeling predicts better oxygenation and rapid growth of metastases in the pulmonary lymphatic vessels as compared to the metastases in the lung parenchyma

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The major cause of death from cancer is metastasis. In the lung, metastases can form in the lymphatic vessels or the lung parenchyma. The presence of cancer metastases in the lung lymphatics indicates poor outcome and rapid disease progression in patients. This is recapitulated in a mouse model, where breast cancer metastases in the pulmonary lymphatics grow larger than metastases in the lung parenchyma, without vascularization. To explain rapid growth of metastases in the lymphatics in the absence of angiogenesis, we have developed a 3D mathematical model of intralymphatic tumor growth. This model is based on deterministic differential equations used to describe avascular tumor growth, adapted to reflect the unique architecture of the lymphatic vasculature. Our model predicts that the cylindrical shape of the lymphatic vessel, which constrains growth of the tumor in two dimensions but allows indefinite growth along the vessel, enables higher oxygen levels throughout the tumor. The greater diffusion coefficient of oxygen in lymph further improves oxygenation of intralymphatic metastases, which do not become anoxic or, depending on vessel diameter, even hypoxic. Improved tumor oxygenation leads to decreased tumor cell death and a rapid increase of metastatic burden in the lymphatics. Importantly, our model further predicts that growth of intralymphatic metastases is exponential. This contrasts the established view that all tumors follow Gompertzian growth kinetics, i.e., tumor growth rate decreases as tumor size increases. These data explain rapid growth of metastases in the absence of angiogenesis and indicate that the lymphatic niche is a favorable environment for metastatic growth.
Poster 14 (25)

Mathematical model of the regulation of the START transition in the budding yeast cell cycle.

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The START transition is a critical regulatory point in the budding yeast cell cycle, where the cell commits irreversibly to a new round of DNA synthesis and cell division. The timing of START is determined by the activation of SBF and MBF, two transcription factors responsible for the synthesis of G1-cyclins (Cln1 and Cln2) and S-phase cyclins (Clb5 and Clb6), which triggering bud initiation and DNA synthesis, respectively. It is well-established that the G1 cyclin Cln3 and a protein Bck2 are key activators of SBF and MBF, and that Whi5 is a key inhibitor of SBF. Although much is known about the molecular interactions of these regulatory molecules, we do not yet have a unified picture of the regulatory mechanisms involved. To this end, we have developed a mathematical model of START based mainly on experimental observations. Where necessary, we make reasonable, justifiable assumptions. By fitting the model to the phenotypes of a wide variety of mutant cells, we are able to estimate the relative strengths of the activatory and inhibitory interactions in the model. The model successfully simulates cell cycle progression in wild-type budding yeast cells and many specific phenotypic details of 136 (out of 143) START mutants, suggesting that our proposed mechanism is a good approximation. With the model in hand, we are able to explore the regulatory network and get a better understanding of how START-control in budding yeast operates.
Poster 15 (29)
The role of glucose-dependent mobilization and priming of insulin granules in the biphasic insulin secretion

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Insulin is the primary regulating hormone of blood glucose, and is produced and released by the pancreatic islet beta cells. A normal beta cell contains an excessive amount of insulin granules, and only a small proportion is ever used. This is even true even under pathological conditions such as diabetes, where demand for insulin is increased but not adequately compensated. The rate limiting steps in insulin secretion, and why the diabetics cannot tap into the vast insulin reserve inside beta cells, are not well understood.

In this study we develop and analyze a mathematical model of glucose-induced insulin secretion from pancreatic islet beta-cells. We assume that insulin granules reside in different pools; also, consistent with recent experimental observations, our model accounts for the fusion of newcomer granules that are not pre-docked at the plasma membrane. In response to a single step increase in glucose concentration, our model reproduces the characteristic biphasic insulin release observed in multiple experimental systems, including perfused pancreata and isolated islets of rodent or human origin.

From our model analysis we note that first-phase insulin secretion depends on rapid depletion of the primed, release-ready granule pools, while the second phase relies on granule mobilization from the reserve. Moreover, newcomers have the potential to contribute significantly to the second-phase. When the glucose protocol consists of multiple changes in sequence (a so-called glucose staircase), our model predicts insulin spikes of increasing height as seen experimentally. In contrast to previous mathematical models, in which the staircase experiment was reproduced by assuming heterogeneous beta-cell activation, we assume a fully homogeneous beta-cells population. In our model the increasing spikes in insulin secretion instead stem from the glucose-dependent increase in the fusion rate of insulin granules at the plasma membrane of single beta-cells. In light of experimental data indicating limited heterogeneous activation when beta-cells are arranged within islets, our findings suggest that a graded, dose-dependent cell response to glucose may contribute to insulin secretion patterns observed in multiple experiments, and thus regulate in vivo insulin release.
Poster 16 (30)

Systems Analysis of Hepatic Metabolic Regulation in Health and Disease

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Human liver acts as a homeostatic controller for maintaining the normal levels of plasma metabolite concentrations by uptake, utilization, storage and synthesis. These hepatic functions are mediated by several metabolic pathways which are regulated at metabolic, signaling and transcriptional levels to provide a robust setting for metabolic regulation. We have used systems biological approach to develop a kinetic model for the first time by integrating the metabolism with the signaling and transcriptional regulatory pathways to analyze the possible scenarios leading to defective hepatic metabolic regulation in developing diabetes. The model consists of metabolic pathways including glucose, fatty acid and amino acid metabolism integrated with their regulation by insulin, glucagon, calcium and mTOR signaling pathways and several transcription regulators such as SREBP, CHREBP, PPAR, CREB, CEBP, PGC1, TRB3, FOXO and AMPK. The overall model consists of 272 rate equations, 170 ODEs and 801 parameters. The analysis of the effect of plasma metabolites (glucose, amino acids and fat) on liver metabolism shows that the chronic change in these metabolite levels by 3 to 4 folds weaken the robustness of hepatic metabolic regulation by reducing insulin sensitivity. Perturbation analysis of the integrated network reveals that the deregulation of PTEN, PTP and IRS are more effective in increasing the hepatic glucose production and release by increasing gluconeogenesis and glycogen breakdown. Moreover we have identified formation of certain double positive and negative feedback motifs in the overall network that can lead to bistable response under certain parameter space and dietary influences leading to diabetic state.
A Comprehensive Model of Cell Cycle Control in Budding Yeast

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The START and FINISH are two most significant transition points of the budding yeast cell cycle. After passing START, cells are committed to DNA replication and after passing FINISH, cells are ready for nuclear division and cytokinesis. In last decade, yeast biologists made a significant progress in unraveling the molecular mechanisms of START and FINISH. To test these hypothetical molecular mechanisms, we have developed a comprehensive cell cycle model of budding yeast. For this large scale model, we use a new modeling framework in which all reactions in the molecular regulatory network are classified into three basic types: protein synthesis and degradation (>C<), phosphorylation and de-phosphorylation (C<->CP), and binding to activator or inhibitor (C+A>C:A). This modeling approach allows us to reduce the number of adjustable parameters and yet continue to explain most phenotypes of mutant strains. The model is successful in explaining the phenotypes of a large number of START mutants, FEAR mutants, Cdc14-oscillatory mutants, and EXIT-from-mitosis mutants.
Computational analysis reveals that spatial distribution of G protein subunits regulates calcium oscillations in HeLa cells

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GPCRs and G proteins regulate several signaling pathways in metazoan cells. Contrary to the traditional model in which the receptor activated G protein subunits stay on the plasma membrane, it has been shown that the βγ complex translocate reversibly from the plasma membrane to internal membranes deferentially depending on the type of γ subunit present in it. Limited understanding of endogenous spatiotemporal dynamics of G proteins makes it challenging to study the role of βγ translocation in modulating downstream signaling activity in a single cell. Since dynamics of βγ complex establish a differential spatial redistribution between cell membranes and is acutely sensitive to the receptor activation state, we hypothesize that it plays a key role in regulating systems level properties of signaling networks. We build an ODE model of βγ mediated calcium oscillations for HeLa cells. Eigen value analysis and simulation suggested that the rate constant of βγ translocation can modulate the duration and frequency of oscillation. Experimentally, a2 adrenergic receptor stimulated calcium oscillations were measured in HeLa cells with different types of G-protein γ subunits. We also quantified the cell to cell variability in a cell population and compared among cell populations. The model predicts the signature kernel distributions of number of oscillations in cell populations with distinct γ subunits compositions. Combination of modeling and live-cell imaging shows that the spatial redistribution of G protein subunits offers a mechanism to control calcium oscillations in a cell.
Poster 19 (51)
Identifying robust sub-network patterns from a database of bistable systems

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An important technique in systems biology is the use of dynamical systems theory to understand and characterize the steady states of biological systems. Bistable systems i.e., those that exhibit (at least) two stable steady states are particularly interesting in biology because they can implement binary cellular decisions such as needed for cellular differentiation and cell cycle regulation. This work focuses on structural features that promote (and ensure) bistability. We hypothesize that the robustness of bistable reaction network structures is dependent on a critical and minimal set of parameters, and that the reactions associated with these parameters form sub-network structures critical for maintaining bistability. To test this hypothesis, we leverage CSPACE, a database consisting of ~3500 bistable chemical reaction systems. Mining the whole database, we endeavor to identify commonly recurring network architectures (sub-systems) in bistable systems that are critical for robustness of stability to parameter fluctuations. To study the consequence of parameter perturbations, we systematically perturb each parameter in each system, conduct eigenvalue analysis, and project out parts of network structures associated with parameters most sensitive to parameter perturbations. The robust sub-networks thus found are also mapped to biological bistable network patterns, through influence diagrams of bistable networks. We generalize influence patterns and their association with robust sub-networks. Such generalization can be useful in implementing bistability in engineered systems where robustness is of particular interest.
Spatiotemporal model of the asymmetric division cycle of Caulobacter crescentus

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The life cycle of Caulobacter crescentus is of interest because of the asymmetric nature of cell division which gives rise to morphologically distinct progeny. One progeny, called the stalked cell is immotile and capable of replication while the other progeny, called the swarmer cell is motile but unable to initiate DNA replication. The underlying cause of asymmetric division is the unequal distribution of proteins to the two halves of the pre-divisional cell. Recent advances in microscopy techniques have allowed experimental biologists to visualize the localization and motion of specific proteins in single cells. While this has led to a better understanding of the regulatory mechanisms that generate the asymmetric cell cycle, the driving force behind the activity and localization of key proteins remain unclear. We have built a spatiotemporal model describing the dynamics of twenty proteins with the aim of providing a holistic understanding of the asymmetric division cycle. We propose that the polymer PopZ shows the Turing pattern of localization. In addition, we describe a molecular mechanism by which the enzyme PleC exhibits bistable transitions between phosphatase and kinase forms. Finally, we show that compartmentalization of the cell is essential for generating asymmetry. Our simulations are in reasonable agreement with experimentally observed protein distributions in wild-type and mutant cells. We are able to reconcile published experimental observations and also make predictions that can be tested in the laboratory.
MSMB: a flexible editor for complex biochemical models

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Building biochemical reaction models is challenging not just because of the intrinsic difficulty of describing biological processes. A modeler has to face the fact that software programs struggle to address many of the modeler’s needs. Writing a model is a creative effort that calls for more flexibility than can be tolerated by today’s biochemical model editors.

We seek to aid modelers with a new version of JigCell (called MSMB, Multi-State Model Builder) that allows editing in a more human-oriented way. In MSMB, at any point in time, the model may contain errors and inconsistencies (e.g., a parameter used in a function is undefined; a reaction is syntactically mis-formed). The model can be left temporarily inconsistent and saved into our tool-specific format. The strict consistency requirements of SBML/COPASI will be enforced only when the modeler decides that the creative part is over and s/he wants to export it into those standard formats. In MSMB users may turn on autocomplete features and notifications to warn of existing errors on-the-fly: all important functions to guide the modeler in the creation of an error-free model. MSMB introduces a new and compact syntax to support multistate species, a key idea that reduces the number of reactions needed to represent certain molecular systems. By reducing the number of reactions, we reduce the cognitive load associated with developing a given model. In a model of the budding yeast cell cycle, the original 59 species and 220 single-state reactions are reduced by 67% using the multistate concept.
Poster 22 (55)
Modeling and Identifying Regulatory Modules in (Glycine max) Soybean Time Series Gene Expression Data using Bayesian Networks

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Much cellular activity is organized as networks of interacting modules. Oftentimes cellular responses can take the form of a network of proteins interacting together under different internal and external conditions. Recently, there has been much interest in reverse engineering these networks using gene expression data. Bayesian approaches have frequently been used to reverse engineer regulatory networks based on transcriptomics data. Gene expression data by itself suffers from high noise and lack of statistical power for inferring causal relationship between genes. Incorporating prior biological knowledge has the potential to improve performance, allowing the production of biologically meaningful networks. It has been shown that incorporating multiple sources of prior knowledge including co-expression and protein-protein interaction data into Bayesian networks creates more predictive and biologically meaningful networks. In this project, a Bayesian network was generated using selected genes from time-series RNA-sequencing-based transcriptomics of developing soybean embryos. A group of genes whose expression changed significantly (p-value < 0.05) in at least one of the time points were identified for Bayesian network learning. We take advantage of multiple data types, including co-expression and co-localization between Arabidopsis homologs of soybean genes from GeneMania (www.genemania.org), and incorporate these data as prior knowledge in order to assess the likelihood of functional linkage between gene pairs. The final Bayesian network yields more biologically meaningful relationships among genes than is obtained from one set of gene expression data only. This is a fresh approach to inferring regulatory network in plant biology.
Poster 23 (56)
Entrainment of synthetic gene oscillators by a noisy stimulus

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Modulation of biological oscillations by external stimuli lies at the root of many phenomena, including maintenance of circadian rhythms, propagation of neural signals, and somitogenesis. While it is well established that regular periodic modulation can entrain an oscillator, a curious phenomenon is that a noisy (rugged) modulation can also robustly entrain oscillations. This latter scenario may describe, for instance, the effect of irregular weather patterns on circadian rhythms, or why irregular neural stimuli can still reliably transmit information. In this work, we investigate experimentally and theoretically the entrainment of an ensemble of synthetic gene oscillators by a noisy stimulus. We quantify cell response using a microfluidic-microscopy framework, and we use delayed feedback models to analyze these cells.
Experimentally validated queueing framework for \textit{Escherichia coli} proteolysis pathways

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We are becoming increasingly aware that a proper understanding of protein degradation (proteolysis) is essential when forming predictive models for many native and synthetic gene networks. A new adaptation of queueing theory predicts that a finite bandwidth of proteolytic pathways leads to meaningful crosstalk between substrates. As one such example, competition for proteolytic resources has been demonstrated to play an essential role in the regulation of the sigma-S mediated stress response pathway in \textit{Escherichia coli} [Cookson et. al, 2011. Mol. Sys. Bio.]. Using queueing theory adapted to biological proteolysis networks, we provide quantitative but intuitive models for these complex competition phenomena. This research includes a joint theoretical-experimental investigation of competition between substrates for the proteases ClpXP & ClpAP in \textit{E. coli}, and the discovery of a correlation resonance, where substrates exhibit extremely strong crosstalk precisely when the system is tuned to the queueing theoretic balance point. To further this biological queueing theory, I developed a discrete stochastic model using enzymatic kinetics and gene networks mimicking coupled proteolytic pathways in \textit{E. coli}. To aid in this endeavor, we are creating a stochastic simulation engine that will become a standard tool for ours and other laboratories. The proteolytic pathways’ dynamics are being tested in vivo using a variety of strains and synthetic circuits, in microfluidic devices. This allows for quantification of individual cell dynamics using fluorescent markers.
Interactions between cytokines and SHH in H. pylori mediated gastritis implicates a novel feedback circuit

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Numerous studies have demonstrated that Helicobacter pylori infection of gastric tissue results in an immune response dominated by Th1 cytokines. Additionally, there is accumulating evidence for the dysregulation of Sonic Hedgehog (SHH) in H. pylori mediated gastritis, a gene primarily known to be involved in embryonic development. However, there are no appropriately detailed mechanistic models that study interactions involving the cytokines, SHH and H. pylori. Lack of comprehensive mechanistic understanding through experimental means, partially attributed to complexity of the circuitry involved, has hindered further rapid progress. Computational models aided by restraints of experimental data can offer an approach to address the difficulty of intuitively analyzing the cross talks and temporal behavior of the network. Using analysis of qrt-PCR data from uninfected and H. pylori infected WT and parietal cell specific SHH knockout mice, we reveal new insights into regulation of certain cytokines by SHH. Focusing on the relationships between SHH, Th1 (IL1ß, IL-12, IFNß) and Th2 (IL-10) cytokines activated by H. pylori, we describe a mathematical model that examines dynamic regulation of these cytokines by SHH during H. pylori infection. The model incorporates previously unknown interactions consistent with qrt-PCR data, and postulates the presence of additional interactions. Our model predicts altered SHH, IL-1ß, NFKB and IL-10 dynamics resulting from a feedback loop that may exhibit oscillatory behaviour. The model suggests a mechanism in support of some of the experimental observations which cannot be explained by existing literature alone. Predictions from our model provide useful insights for designing more targeted in-vivo and in-vitro experiments.
Poster 26 (61)
A numerical method to solve PDEs modeling the activity spread of small GTPases after spine stimulation

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Long term potentiation (LTP), a cellular correlate for learning and memory, is associated with specific and non-specific modifications to excitatory synapses. Different spread patterns of small GTPases activity on the membrane after spine stimulation have been related to the specific and non-specific modifications during LTP. For example, after stimulation, the activity of Cdc42 displays a persistent localization to the stimulated spine. In contrast the activity of RhoA and HRas spread out of the activated spine along the dendritic shaft reaching adjacent spines. The mechanisms accounting for such spread differences are not well understood. It is known, however, that small GTPases work as molecular switches and whereas their active form is found and diffuses on the membrane, their inactive state diffuses in the cytosol. Furthermore the geometry of the spine is believed to be important for the establishment of the observed activity distributions. In order to formulate and evaluate mathematical models accounting for the different small GTPase activity profiles, we present a novel method to solve reaction-diffusion equations on complex geometries, coupling diffusion on the membrane with diffusion in the cytosol. Dynamics on the membrane are solved using the Closest Point method, an embedding finite differences approach. Diffusion in the cytosol is solved using finite differences setting appropriate boundary conditions. Our approach is second order accurate in the grid spacing. We use the technique to implement a mathematical model (Wave-Pinning) that could account for the persistent localization of Cdc42 activity to the spine.
Poster 27 (62)
Mathematical framework for the interstitial pressure calculation inside a solid tumor with a heterogeneous vascular network

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Solid tumors switch from the benign phase to the malignant phase by initiating a phenomenon called angiogenesis. Angiogenesis is a multiscale phenomenon that in cellular level is regulated by many cells and proteins. Moreover, angiogenesis causes interstitial pressure elevation inside the tumor by forming leaky and weak vascularization. Some recent findings show that interstitial pressure inside the tumor has critical effects on signal transduction in tumor cells and create different pathways at the cellular level of the tumor. Interstitial pressure in a tumor with homogeneous vasculature has been widely studied. However, a physiologically relevant heterogeneous vascular network model is essential because the tumor environment is heterogeneous and its vascular irregular. The purpose of this paper is to provide a framework to calculate the interstitial pressure in a heterogeneous vascular network.

First, we model the vascular network, based on the tumor physiological phenomena such as, tumor growth, angiogenesis at the tumor periphery, and the vascular regression inside the tumor due to the tumor cell stress. Results show an irregular network with high microvascular density at the tumor periphery and a few functional vessels inside the tumor that are in agreement with experimental data.

Second, having set vascular network, interstitial pressure can be calculated by utilizing transport phenomena equations including continuity, Darcy’s law and Starling’s law.

Results demonstrate a maximum interstitial pressure inside the tumor close to the functional vessels; however, this maximum interstitial pressure is about 20% less than the maximum interstitial pressure has been found in homogenous vascular model.
Poster 28 (63)
A user-friendly computational platform for stochastic model inference and analysis

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With the increasing availability of single cell, time-course data for biological networks, there exists a growing demand for the inference and exploration of stochastic models that can properly describe the nonlinear and noisy dynamics characteristic of these networks. However, this work is still typically done using custom computer code, due to a distinct lack of user-friendly software with sufficient ability. We aim to provide a software package which unifies these processes in a coherent framework that can be used with little to no programming experience. We implement through graphical user interfaces commonly desired functions such as statistical model inference based on experimental data, network robustness measurements, and intelligent plotting of results. All of these functions are supported by powerful routines designed to take advantage of multicore and GPU computing environments, which are increasingly prevalent in modern machines.
Poster 29 (64)
Putting the circadian clock together: using high performance computing to investigate coupling in the suprachiasmatic nucleus

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Circadian rhythms are endogenous oscillations, seen in many physiological processes, with periods of roughly 24 hours. In mammals, rhythms throughout an organism are controlled by a master pacemaker comprised of the roughly twenty thousand neurons of the suprachiasmatic nucleus (SCN) in the hypothalamus. Many great mathematical models have provided insights into the mechanisms behind the clock over the years, helping to advance the field of circadian research. Now, with advances in high performance computing, we are able to present the next generation of SCN modeling, with a level of detail that was not previously possible. This new multi-scale “supermodel” of the SCN is able to track both the electrical activity, at the scale of individual ionic currents and action potentials, and molecular clock rhythms, at the level of individual protein and complex concentrations, in every cell of the SCN. All of these behaviors are simulated with millisecond resolution. This is a powerful tool for investigating the connections between the molecular oscillations and electrical activity rhythms in individual cells, as well as the coupling between individual SCN neurons. While these details are difficult to probe simultaneously in a wet lab, we show that the model can provide powerful intuition, and make predictions which then can be used to inform wet lab experiments.
Metabolic reprogramming in metastatic colon cancer

Prof. SHEN, Xiling

Cornell University

Colorectal cancer (CRC) is a leading cause of cancer death worldwide. As 5-year survival for early stage CRC is ~90% vs. ~8% for metastatic CRC, it is critical to develop new therapeutics against metastatic CRC. However, drug candidates that are effective against CRC cells in vitro or in subcutaneous (under the skin) xenograft mouse models have routinely failed to show consistent efficacy against metastatic CRC in clinical trials. The high failure rates suggest that CRC cells may have been reprogrammed to become more chemoresistant by their in vivo tumor microenvironments.

To understand how CRC metabolism responds to different tumor microenvironment, we used high-resolution mass spectrometry to carry out extensive quantitative characterization of the metabolome specific to in vitro culture, subcutaneous, orthotopic, and liver metastatic tumors of multiple CRC subtypes. We performed metabolic flux analysis on CRC cells cultured in vitro and then computationally derived the fluxes in metastatic CRC based on alterations in metabolite and enzyme levels between in vitro cultures and in vivo tumor cells. A computational model of CRC metabolism in different tissue microenvironments was then built based on the metabolomics measurements. Simulation of the model revealed metabolic reprogramming of metastatic CRC cells and potential metabolic liabilities that could be targeted for future therapeutic strategies.
Failure to maintain airway surface liquid homeostasis impacts proper mucociliary clearance leading to pulmonary diseases such as cystic fibrosis. Airway hydration requires a balance between ion secretion and absorption. Ion transport is disrupted in cystic fibrosis due to the introduction of functional mutations in the chloride ion transport protein cystic fibrosis transmembrane regulator. These mutations result in a reduced ability to secrete chloride and water into the airway surface liquid. A nucleotide regulatory system in the airway surface liquid restores hydration under normal conditions by modifying ion transport. Our central hypothesis is that airway surface liquid height is controlled by extracellular nucleotide concentrations (ATP and adenosine) that affect water fluxes by regulating ion transport. Here we present a computational model of airway surface liquid homeostasis via purinergic regulation of ion transport in epithelial cells. Using this model, we show that changes to the apical membrane permeability to chloride and sodium ions are necessary for increased airway surface liquid height observed under increased ATP and adenosine concentrations. We also present curves describing the relationships between membrane permeability to chloride and sodium ions and ATP and adenosine concentrations. Once the specific mechanisms of purinergic regulation of ion transport and airway surface liquid height are known, we will use our model to propose therapeutic techniques to improve airway hydration and mucociliary clearance.
Poster 32 (76)
Transcriptional delay stabilizes bistable gene networks

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Transcriptional delay can significantly impact the dynamics of gene networks. Here we examine how such delay affects bistable systems. We investigate several stochastic models of bistable gene networks and find that increasing delay dramatically increases the mean residence times near stable states. To explain this, we introduce a non-Markovian, analytically tractable reduced model. The model shows that stabilization is the consequence of an increased number of failed transitions between stable states.

Poster 33 (86)
Reciprocity between sugar dose and duration of G protein activation in Arabidopsis thaliana

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Cells continuously adjust their behavior in response to changing environmental conditions. Both intensity and duration of external signals are critical factors in determining what response is initiated. Therefore, cells must be capable of processing more than binary (on/off) input. To understand how this signal processing is achieved, we studied AtRGS1-mediated, glucose response of Arabidopsis. By combining experiments with mathematical modeling, we discovered a “dose-duration reciprocity” in which high or low sugar concentrations induce maximal pathway activation, but require distinct exposure duration to achieve steady state. We demonstrate dose-duration reciprocity is achieved through orchestrated action of three kinases (AtWNK1, AtWNK8, AtWNK10) acting on distinct time scales and activation thresholds. Specifically, we find a high concentration of D-glucose rapidly signals through AtWNK8 and AtWNK10, whereas a low, sustained sugar concentration slowly activates pathway through AtWNK1. This dose-duration reciprocity allows cells to respond to both the intensity and persistence of energy resources.
Interrogating the yeast pheromone response using transient and periodic stimuli

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The ability of cells to respond appropriately to stimuli is critical in organismal development and for maintaining cellular homeostasis in changing environmental conditions. The pheromone induced mating response in Saccharomyces cerevisiae is a model system for understanding signal transduction through MAP kinase cascades, including those activated in response to growth hormones and stress in higher eukaryotes. In the case of the mating pathway in S. cerevisiae, the constituent proteins involved and their interactions have been identified, but what remains is to build a systems-level understanding of the pathway to accurately predict cellular response to various dynamic regimes of pheromone stimulus.

Here, we use an engineering approach to reveal the predominant mechanisms that give rise to mating specific gene expression in a population under a variety of conditions. A fast maturing, short-lived GFP serves as a reporter that can capture the induction and attenuation phases of gene expression as a result of a pulsatile stimulus. Microfluidic devices are used to precisely control the pheromone stimulus for various periods and at low and high concentrations. The population-averaged gene expression to either transient or periodic stimulus revealed three distinct characteristics of the response: 1) persistence of gene expression after withdrawing pheromone, 2) amplitude and 3) long-term adaptation. A model capable of recapitulating the observed behaviors requires four regulatory motifs: slow release of the transcription factor Ste12 from DNA, positive feedback through Ste12 autoregulation, negative feedforward by pheromone initiated Ste12 degradation, and deactivation of Ste12 through binding to transcriptional inhibitors. Disrupting each individual motif through genetic manipulation has led to refinement of the model while revealing the predominant motifs that give rise to cellular response.
Poster 35 (88)
Unrestrained Ga signaling Through PI3 Kinase Results in Mislocalization of Septins and Loss of Gradient Tracking in S. cerevisiae.

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Haploid S. cerevisiae respond to mating pheromone with a GPCR coupled to the large G-protein, Gpa1. At high pheromone concentrations yeast form a pointed mating projection with the polarity machinery at the tip, while the base of the projection is bounded by scaffolding proteins known as septins. At intermediate concentrations of pheromone, yeast elongate in the direction of increasing pheromone concentration, tracking the gradient. Gradient tracking requires Sst2, the GAP for the large G-protein Gpa1. Here we examine the role of septins in gradient tracking by comparing wild type yeast to a non-tracking sst2Δ strain using live cell microscopy in a microfluidic device. We have found that in cells undergoing chemotropic growth, septins are deposited along the periphery of the cell, and are excluded from sites of polarized growth. In cells lacking Sst2, septins are not deposited on the periphery and are instead localized to sites of polarized growth. Localization of the GAP to the periphery of cell is not required for proper septin deposition suggesting that excess Gpa1 activity at the endosome, where activated Gpa1 signals through the class III PI3 Kinase, may be the cause of the defects in sst2Δ. Disruption of PI3 Kinase activity was able to rescue septin deposition and gradient tracking in an sst2Δ background. We conclude that the sst2Δ defects in septin deposition and gradient tracking are due to excess PI3 Kinase activity stimulated by an overabundance of Gpa1-GTP at the endosome.
Poster 36 (89)
Inverse Gillespie: Inference of Stochastic Mechanisms

Dr. CHATTOPADHYAY, Ishanu ¹; Dr. KUCHINA, Anna ²; Prof. SUEL, Gurol ²; Prof. LIPSON, Hod ¹
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Gillespie’s stochastic simulation algorithm (SSA) is an accurate procedure for predicting time-evolution of stochastically interacting populations of chemical species given the systemic reactions; defining a computational approach to solve the intractable probabilistic master equation. However, the inverse problem of de novo inference of stochastic biochemical networks from experimental data is still largely open. Researchers are now able to estimate the number of specific macromolecules within a cell, prompting a need for tools that explicitly model stochastic phenomena.

We present a new principle to reverse-engineer observed expression time series for de novo structural identification along with estimation of reaction propensities.

We only need intermittent measurements of population counts of the participating species, and may skip hundreds or thousands of reactions between successive measurements.

For a system evolving stochastically, with the population counts of the interacting chemical species or agents observed intermittently, we rigorously establish that the set of relative update vectors approximately define a convex bounded polytope. The direction cosine of each vertex of this polytope coincides with the population update realized by a major driving reaction. Furthermore, this alignment is independent, up to a certain point, of the degree of intermittency of the observations. We show that these polytope vertices, and hence the direction cosines of the hidden dominant reactions, may be identified from the observed population time series alone, with no a priori system knowledge.

Using our approach we infer interaction of key regulators in the competence dynamics of B. subtilis.
Noise induced oscillations in biological circuits with only positive feedback

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Noise can have significant effect on the dynamics of biological systems. For instance, noise can induce oscillations in biological circuits that do not otherwise exhibit oscillations when the deterministic dynamics is considered. An example of this case are certain excitable systems [1] in which small perturbations (noise) can kick the system off of a stable fixed point and cause it to take a long excursion around an unstable fixed point before the system returns back to the stable fixed point. Near Hopf bifurcation, (intrinsic) noise in such systems can induce oscillations around the unstable spiral before the system comes back to the stable fixed point. Another example of noise induced oscillations in biological circuits are the long lived (unstable) oscillations in repressilators with even number (six or more) of genes [2]. The excitable system [1] discussed above consist of four chemical species. The topology of the circuit is such that a negative feedback is coupled with a positive feedback. On the other hand, the repressilator model with even number of genes [2] consist of only positive feedback but requires six or more genes in the circuit to exhibit noise induced oscillations. In this study, we are interested in knowing if it is possible to generate noise induced oscillations in circuits with smaller number of species (less than six) and with only positive feedback. We would also like to know if the negative feedback is absolutely required for an excitable system? Can a system with only positive feedbacks behave like an excitable system? For this we are studying circuits with three chemical species with only positive feedback. For this purpose, we are using both numerical and analytical techniques in our investigation.

Poster 38 (101)
Comparing electrophysiological models of M1 and M4 intrinsically photosensitive retinal ganglion cells

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Intrinsically photosensitive retinal ganglion cells (ipRGCs) respond to light through the photopigment melanopsin and are responsible for mediating subconscious visual processes such as pupil resizing, melatonin secretion, and entrainment of the circadian clock. Using voltage and current clamp recordings, we develop models of the electrophysiological properties of two subtypes of ipRGC, M1 and M4, which are known to vary significantly in both form and function. These models are simulated both as point cells and with realistic morphologies. In addition, the modeled cells are tiled spatially and passed an image as input in order to quantify what each of the two subtypes is capable of “seeing.” Finally, the cells are given rod-cone input and linked to a preliminary model of melanopsin phototransduction to more completely simulate the external contributions to ipRGCs.
Poster 39 (102)
Aggregation Connector: A Tool for Building Large Molecular Network Models from Components

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The ever-growing size and complexity of molecular network models makes them difficult to construct and understand. Our approach to modeling is to build large models by combining together smaller modules, making them easier to comprehend. At the base, the smaller models (called modules) are defined by small collections of reactions. Modules connect together to form larger modules through clearly defined interfaces. We present the Aggregation Connector, a software tool that supports large-scale molecular network modeling.
Poster 40 (2)
Simulating period variation in glucose-compensated Neurospora circadian clock

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Robust circadian (daily) rhythms play a vital role in an organism’s functions and in anticipation of changes in its environment. Circadian oscillations are believed to arise from negative feedback loops formed by transcription, translation, and post-translational interaction of core clock components. Recent experiments identified a global transcription repressor, CONIDIAL SEPARATION-1 (CSP-1), as a key player in circadian clock and glucose-compensation mechanism of filamentous fungi Neurospora crassa. Based on these findings, we have modified the model of N. crassa circadian clock previously developed by Hong et al (2008) to include CSP-1 as an important element of the core clock machinery. This new model accurately reproduces glucose compensation behavior as well as period variation observed in available overexpression experiments, and provides insights for further experimental studies of Neurospora circadian clock. In particular, the model simulations reveal that the FREQUENCY (FRQ) protein abundance in the nucleus plays a crucial role in controlling the period variation. In fitting with the experimental data, our model predicts high cooperativity of WHITE COLLAR-1 (WC-1) activation of frequency (frq) gene transcription and low cooperativity of CSP-1 repression of WC-1.
How phenotypes shape cell-to-cell variations of protein abundances?

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Cell-to-cell variations in the protein abundances, even in a genetically identical cell population, are ubiquitous. Recent experiments casually relate the variations in protein concentrations to the specific cell phenotypes. In hematopoietic stem cells for example, differences in the protein abundances can produce distinct lineage commitment. However it is not clear to what extent a given phenotype influence and shape the single cell distributions of the relevant proteins. Using Maximum Entropy based method we address this question in the context of Escherichia coli (E. coli) chemotaxis. We show the nearly perfect nature of adaptation of E. coli cells to a change in nutrient concentration in the medium and the experimentally observed distribution of adaptation time in individual E. coli cells enforce co-variations between protein abundances involved in the chemotaxis signaling network. However, our calculations also show that the observed chemotactic response can accommodate a much wider variation in protein abundances in single cells compared to the distributions observed in experiments. This suggests that additional constraints imposed by gene regulatory processes. We found that Gaussian distributions of protein abundances consistent with average values and pairwise correlations in protein abundances measured in an E. coli cell population can remarkably generate the chemotactic response observed in single cells. Thus, the observed long tails or deviations from the Gaussian distribution in the actual distributions of protein abundances could arise to satisfy constraints imposed by non-chemotactic processes.
Multiple steady states in a mathematical model for interactions between T cells and macrophages

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Interactions between T cells and macrophages can be described by a system of four ODE due to Ruth Lev Bar-Or. The unknowns are concentrations of Th1 and Th2 cytokines produced by the two types of cells. In the original paper it was shown by numerical simulation that this system can admit two stable steady states for given values of the parameters. There is a simplified model with two parameters which already exhibits many of the dynamical features of the full system. More recently I showed that the full system admits four stable steady states for certain values of the parameters. These were originally found by numerical experimentation and their existence and stability were then proved rigorously. The method is to use the numerical results to guess where the steady states are approximately and then to construct a fixed point argument. Questions which are still open, analytically and numerically, are whether there can be even more steady states and whether there can be periodic solutions. I also do not know whether states of the immune system with different strengths of Th1 or Th2 dominance have been observed experimentally.


Computer simulations of the mouse spermatogenic cycle

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A fundamental feature of mammalian spermatogenesis is the continual production of sperm throughout reproductive life. The spermatogenic cycle describes the periodic development of male germ cells, which occurs every 8.6 days in the mouse. Each cycle can be divided into Stage I to XII based on well-defined associations of germ cells on seminiferous tubule cross-sections. The periodic patterning of germ cells results from multiple cellular events including interactions, differentiation, proliferation, apoptosis, and movement. However, the precise action of germ cells that leads to the emergence of different tissue patterns remains undefined. We develop an agent-based model to simulate the mouse spermatogenic cycle on a cross-section of seminiferous tubules over a time scale of hours to years. The model depicts a tubule cross-section in a regular grid. Ten types of germ cells are included ranging from spermatogonia to spermatids. Kinetic parameters for differentiation, proliferation, apoptosis, and movement, are estimated from static and dynamic imaging and irradiation experiments. Our model elaborates the temporal-spatial dynamics of germ cells, allowing us to trace individual cells as they change state and location. By manipulating cellular events either individually or collectively in silico, the model allows us to predict the causal events to the abnormal morphology observed in various genetic and environmental perturbations. Importantly, the model provides a mechanistic understanding of how tissue morphology and sperm production are achieved, thus opening new possibilities for manipulating cellular behaviors and interactions to ensure the continual production of sperm.
Optimization and model reduction in the high dimensional parameter space of a budding yeast cell cycle model

Dr. OGUZ, Cihan; Dr. TYSON, John; Dr. BAUMANN, William; Dr. LAOMETTACHIT, Teeraphan; Dr. CHEN, Katherine; Dr. WATSON, Layne

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Parameter estimation from experimental data is critical for mathematical modeling of protein regulatory networks. For realistic networks with dozens of species and reactions, parameter estimation is an especially challenging task. In this study, we present an approach for parameter estimation that is effective in fitting a model of the budding yeast cell cycle (comprising 26 nonlinear ordinary differential equations containing 126 rate constants) to the experimentally observed phenotypes of 119 genetic strains carrying mutations of cell cycle genes. Starting from an initial guess of the parameter values, which correctly predicts the phenotypes of only 72 genetic strains, our parameter estimation algorithm quickly improves the success rate of the model to 105-111 of the 119 strains. The algorithm combines two search and optimization strategies. First, we use global sampling to explore a region surrounding the initial guess. Next, we perform an evolutionary search that iteratively improves parameter values in terms of their success rate in capturing experimental constraints. In addition to producing highly successful combinations of parameter values, we analyze the results to determine the “most critical parameters” and the “most competitive constraints”, which provide biological insights into the model. Conversely, the “least critical parameters” and “least competitive constraints” suggest ways to reduce the computational complexity of the optimization. Our approach proves to be a useful tool to help systems biologists fit complex dynamical models to large experimental data sets.
Poster 45 (37)
Dynamics of Autophagy and Apoptosis Interplay in Cancer Cells: Mathematical Modeling and Experimental Observations

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Autophagy is a self-degradation process in cells: damaged proteins and organelles are sequestered within double-membrane vacuoles, called autophagosomes, where they are degraded into re-usable metabolites. This process can provide a cell with raw materials and ATP for its survival under stressful conditions. Treating breast cancer cells with endocrine therapy agents (Tamoxifen or Fulvestrant) increases the rate of formation of autophagosomes. We view autophagy as a decision-making module which determines cell fate (survival, apoptosis or autophagic cell death) based on the stress induced by therapeutics. In endocrine-resistant cells there should be some mechanisms to reinforce the ability of autophagy to reduce the stress induced by endocrine therapy agents. In a system biology approach we are combining mathematical modeling with experiments to verify our proposed dynamic model for the cell fate decisions involving autophagy. Starting from an interaction diagram that represents the signaling network controlling autophagy and apoptosis, we derive a set of Ordinary Differential Equations that reproduces in silico the dynamical responses of breast cancer cells to stress in vitro. Using endocrine-resistant breast cancer cell lines, we are measuring the dynamical properties of autophagic response to evaluate the model’s predictions and to provide more accurate parameter values.
Signaling Pathway Prediction from Human Interactome Data

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Signaling pathways represent the information-passing mechanisms of the cell, and usually begin with the activation of a receptor molecule and end with the regulation of specific target genes. Databases such as KEGG and NetPath use extensive manual curation to construct high-quality representations of the signaling pathways. While these pathways are often high-quality, they are laborious to construct and require constant manual updating. Partially automating this process would help improve such knowledge-based resources. Additionally, suggesting proteins potentially associated with a signaling pathway might provide novel biological insight and suggest follow-up experiments to perform.

To this end, we have developed a method to predict signaling pathways from a human interaction network when we are given subset of the proteins known to be involved in the pathway. Specifically, suppose we know the signaling receptor and the transcription factors that are activated in response to an external stimulus. From this set of proteins, we wish to discover the signaling pathway by identifying the intermediary proteins as well as the connections between proteins.

Our method first assigns a score to all proteins that indicates how likely they are to be activated by the signaling receptor(s), and then identifies highly-probable paths connecting the signaling receptor(s) to the downstream transcription factors. We apply our method to 16 manually-curated signaling pathways from NetPath, and find that it consistently outperforms a number of previously-published algorithms in terms of correctly recovering the NetPath pathways. Additionally, we find a number of proteins and interactions that are potentially missing from the NetPath pathways.
Poster 47 (46)
Top-Down Network Analysis to Drive Bottom-Up Modeling of Physiological Processes

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Top-down analyses in systems biology can automatically find correlations among genes and proteins in large-scale datasets. However, it is often difficult to design experiments from these results. In contrast, bottom-up approaches painstakingly craft detailed models that can be simulated computationally to suggest wet lab experiments. However, developing the models is a manual process that can take many years. These approaches have largely been developed independently.

We present Linker, an efficient and automated data-driven method that can analyze molecular interactomes to propose extensions to models that can be simulated. Linker combines teleporting random walks and k-shortest path computations to discover connections from a source protein to a set of proteins collectively involved in a particular cellular process.

We evaluate the efficacy of Linker by applying it to a well-known dynamic model of the cell division cycle in budding yeast. Compared to other state-of-the-art methods, subnetworks computed by Linker are heavily enriched in GO terms relevant to the cell cycle. Finally, we highlight how networks computed by Linker elucidate the role of a protein kinase (Cdc5) in the mitotic exit network of a dynamic model of the cell cycle. Source code and datasets are available on the supplementary website.
Poster 48 (47)
Cross-talk and Information Transfer in Signal Transduction

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Bacterial and mammalian cells have many signaling pathways that are simple phosphorylation relays. Many of these signaling pathways interfere with one another, and there has been a significant effort expended on understanding how the effects of this cross-talk could be minimized. In this work we take a different tack, and use information theory to study whether cross-talk is necessarily deleterious to information transfer. We find that in many physiologically plausible situations cross-talk does not degrade information transfer leading to the hypothesis that the signal transduction machinery may make active use of it in some situations. In other conditions we find that cross-talk does in fact degrade information and present some evidence from the literature that this may be happening in some bacterial signaling systems.
Poster 49 (48)
Particle-based Simulation of Shallow Chemical Gradient Sensing in Yeast

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During mating, yeast cells must measure the direction of highest pheromone concentration and grow in that direction towards a mate; a clear evolutionary advantage lies in rapid and accurate measurement of the pheromone gradient. Yeast use a spatial detection mechanism. In a gradient more receptors will be bound on one side (the front) than another (the back). In cases of shallow gradients (0.5 nM/um) centered at the Kd of the receptor, this difference may be 100 +/- 50 bound receptors; the error arises from stochastic binding and unbinding. Since the noise is on the same scale as the signal, a non-trivial mechanism for measuring is needed: time-averaging. Fast binding and unbinding rates allow for frequent sampling and hence, a rapid & accurate measure of the gradient. Contradictory to this expectation, however, the yeast pheromone receptor is suspected to have poor binding (1.6*10^5 1/M*s) and unbinding (10^-3 1/s) rates. With these rates, resampling the environment just once takes over 15 minutes. We aim to demystify this paradoxical model of gradient sensing.

We have created a computer program to simulate individual molecules to stochastically solve the reaction-diffusion equation (discretely in time and continuously in space). To simulate second-order reactions, we independently customize the binding radius and the time step of the simulation. For spatial accuracy, our binding radius is equal to the size of the receptor, and the diffusion step size is on the same scale (by choosing a small time step). Experimentally measured reaction rates and diffusion constants are also used.
Poster 50 (49)

Transitions between endocrine response and resistance states on the breast cancer landscape

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¹ Virginia Tech

Endocrine therapy targeting estrogen receptor pathway is the most common treatment on breast cancer. However, cancers under endocrine therapy usually develop resistance robustly, leading to a major problem in breast cancer treatment. In clinical, two strategies are useful to deal with acquired endocrine resistance: sequential treatment, in which second-line endocrine drugs are used to gain another response; intermittent treatment, by imposing a ‘drug holiday’ between endocrine treatments. However, our previous understanding of their mechanisms is mostly by intuition. Here we presented a mathematical model of the transitions among three different estrogen sensitivity phenotypes in breast cancer. As a simple example showing endocrine response and resistance state transitions during E2 manipulations, the model was mapped into a potential landscape that provides a global view of dynamic properties of the breast cancer system. It is shown that the breast cancer landscape can be reshaped by population selection, which is a crucial force in promoting acquired resistance. In addition, a simplified state transition model grounded on the most possible routes of transitions on the breast cancer landscape was built and evaluated. Optimum treatment conditions of both sequential and intermittent treatments to overcome acquired endocrine resistance were investigated. The guidelines and findings in this study can be generalized to investigate treatment strategies, and improve treatment efficiencies in breast cancer as well as other types of cancer.
Poster 51 (79)

Ranking predictions for validation: An example from an antiestrogen sensitivity model in breast cancer

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Experimental observations of complex biological systems can be quantitatively understood using mathematical models that enable in-silico ‘experiments’ and generation of testable predictions. When considering model-based predictions, the question of how to assess and rank the reliability of the predictions, given the model and the data upon which it is based, naturally arises. It is also important to assess and rank the most unreliable predictions, as these lead to the experiments containing the most information for improving the model. Here we investigate a simple framework for evaluating the reliability of model predictions using a mathematical model of anti-estrogen sensitivity in breast cancer that explains how estrogen receptor alpha (ERα) knockdown affects the unfolded protein response (UPR) as well as how its knockdown, when combined with anti-estrogen therapy, synergistically reduces cell proliferation compared to anti-estrogen treatment alone. The model can be fit with an ensemble of parameter sets. Although the resulting parameterized models reproduce the experimental data, the parameter sets exhibit a large divergence. A scatter plot of a predicted phenotype versus the relative parameter set distance is used to evaluate the reliability of different model predictions. By ranking the predictions according to reliability, several reliable predictions were chosen for model-validation experiments. These validation experiments matched the model’s predictions, supporting the model’s usefulness. This framework can be generalized to other models for quantitatively ranking and selecting predictions for model validation and improvement.
Cells undergo specialized cell divisions called meiosis to generate haploid spores or gametes. In contrast to mitosis, DNA replication during meiotic program is followed by an extended prophase I and two consecutive M phases. During prophase I, cells undergo homologous recombination by initiating DNA double strand break (DSBs). This halts the progress into M-phase by activating the recombination checkpoint which in budding yeast inhibits the meiosis specific transcription activator Ndt80 until all the DSBs are repaired. In this work we have studied how the exit from prophase I is controlled by systems level feedback loops. Mathematical modelling of the regulatory network that control prophase I to metaphase I transition revealed the bistable characteristics of the transition which was experimentally validated. The analysis shows that the feedback regulation of both synthesis and degradation machinery in prophase 1 provides a robust control of arrest and resumption of meiosis.

Reference:
Poster 53 (83)
Usable Software Tools for Computational Biology

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We present usable tools for fast simulation and exploration of biochemical networks modelled as ODEs. Our goal was to create tools that bring the power of numerical algorithms to the hands of experts in computational biology and design those tools around the user (user centered design). Usability is often overlooked in software development despite being well studied by computer scientists and industrial engineers. PET is currently being used by computational biologists on a daily basis and is the software tool used to develop the budding yeast model from Chen and Tyson, et al.. PET is the prototype for the tools we present in this poster and features undo/redo, parameter optimization, a tight loop between user input and simulation, plotter, etc. Principles of user interface design such as the structure principle, simplicity principle, visibility principle, and feedback principle were used to construct the user interface.
Poster 54 (41)

Theoretical Analysis of Minimal Models of Biochemical Oscillators

Prof. HONG, Christian \(^1\); CAICEDO-CASSO, Angelica \(^1\); Prof. LIM, Sookkyung \(^1\)

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Biological systems exhibit numerous oscillatory behaviors from cell division cycles to circadian rhythms. These autonomous oscillators contain complex feedbacks with nonlinear dynamics that enable spontaneous oscillations. The detailed nonlinear dynamics of such systems in varying parameter space remain largely unknown. Mathematical modeling and synthetic biology are useful tools to investigate nonlinear dynamics that may arise from different feedback circuits and nonlinear functions. In this report, we theoretically analyzed four minimal ordinary differential equation (ODE) models that generate autonomous oscillations. These models are: 1) Goodwin oscillator that has three variables, 2) two-variable substrate-depletion (autocatalytic) model, and 3) & 4) two-variable models that contain both negative and positive feedback loops. For each model, we used one- and two-parameter bifurcation analyses to find a reasonable region of parameter space that generate spontaneous oscillations, and investigated changes of period and amplitude as a function of each parameter in the system. Furthermore, we performed local sensitivity analysis to identify sensitive parameters from each model. Our analyses show that small differences in feedback circuits result in dramatic changes in nonlinear dynamics of the system. In our future work, we plan to design synthetic circuits in a model filamentous fungus, Neurospora crassa, and validate our predictions.
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Wednesday, August 14, 2013

**Virginia Bioinformatics Institute (VBI)**  
9:00 AM - 12:00 PM Registration - VBI Lobby  
12:40 - 1:00 PM Opening Remarks and Welcome

**Session I**  
1:00 - 1:45 PM The Challenges of Proliferative Control  
1:45 - 2:30 PM Combining experiments and modeling to understand actin dynamics during endocytosis and cytokinesis  
2:30 - 3:00 PM Break, VBI Lobby

**Session II**  
3:00 - 3:45 PM Mechanism of cell polarization in budding yeast  
3:45 - 4:05 PM Distinct actin networks dictate traction peak oscillation of focal adhesions  
4:05 - 4:25 PM Dynamic modeling of yeast meiotic initiation  
5:30 - 7:30 PM Dinner, Dietrick Dinning Hall (D2)

**Session III**  
9:00 - 9:45 AM Cell cycle control by a minimal Cdk network  
9:45 - 10:05 AM Examining Boolean network approach as a modeling approach for protein networks: Fission yeast cell cycle as an example  
10:05 - 10:25 AM Observability of complex biological systems  
10:25 - 10:50 AM Break, VBI Lobby

**Session IV**  
10:50 - 11:40 AM Regulatory networks and cellular rhythms: The cell cycle and the circadian clock  
11:40 AM - 12:00 PM Circadian-gated cell division cycles in Neurospora crassa  
12:00 AM - 12:10 PM Conference Group Photo  
12:10 - 2:00 PM Lunch, Dietrick Dinning Hall (D2)

**Session V**  
2:10 - 2:55 PM Bistability and Trigger Waves in Mitosis  
2:55 - 3:15 PM The State of Silence  
3:15 - 3:35 PM Break, VBI Lobby

**Session VI, Student Travel Prize Talk Session**  
3:35 - 4:50 PM Specification of cell size and control of size heterogeneity by mTOR -dependent modulation of growth rate prediction

**Friday, August 16, 2013**

**Session VII**  
9:00 - 9:45 AM Periodically probing the pheromone response of yeast  
9:45 - 10:05 AM A dynamic expression circuit in single basal-like breast epithelial cells  
10:05 - 10:30 AM Break, VBI Lobby

**Session VIII**  
10:30 - 10:50 AM Mono- and multi-valent ligation of the BCR exhibit differential dependence upon Syk and Src family kinases  
10:50 - 11:10 AM Information flow defines code converting PI3K and MAPK signaling to Proliferation  
11:10 - 11:30 AM Cell type-specific processing of signaling information by NF-xB dynamics

**Session IX**  
11:30 AM - 12:30 PM Forum for Interdisciplinary Research & Education  
12:30 - 2:30 PM Lunch, Dietrick Dinning Hall (D2)

**Session X**  
2:30 - 3:15 PM Defining the kinetochore mechanical properties important for regulation of mitotic chromosome dynamics in PtK1 cell  
3:15 - 3:35 PM The Membrane Environment Can Promote or Suppress Bistability in Cell Signaling Networks  
3:35 - 3:55 PM Break, VBI Lobby

**Session XI**  
3:55 - 4:40 PM Mechanisms of length regulation of flagella in Salmonella  
4:40 - 5:00 PM Modeling endocrine resistance in breast cancer  
5:00 - 5:05 PM Closing Remarks  
6:00 - 9:00 PM Evening Banquet, Inn at Virginia Tech